PROTEASE INHIBITORS

FIELD OF THE INVENTION

This invention relates in general to the use of 4-amino-azepan-3-one protease inhibitors, particularly such inhibitors of cathepsin S, in the treatment of diseases in which cathepsin S is implicated, especially treatment or prevention of autoimmune disease; treatment or prevention of a disease state caused by the formation of atherosclerotic lesions and complications arising therefrom; and diseases requiring inhibition, for therapy, of a class II MHC-restricted immune response, inhibition of an asthmatic response, inhibition of an allergic response, inhibition of immune response against a transplanted organ or tissue, or inhibition of elastase activity in atheroma; and novel compounds for treating same.

BACKGROUND OF THE INVENTION

Cathepsins are a family of enzymes that are part of the papain superfamily of cysteine proteases. Cathepsins K, B, H, L, N and S have been described in the literature.

Cathepsins function in the normal physiological process of protein degradation in animals, including humans, e.g., in the degradation of connective tissue. However, elevated levels of these enzymes in the body can result in pathological conditions leading to disease. Thus, cathepsins have been implicated as causative agents in various disease states, including but not limited to, infections by pneumocystis carinii, trypsanoma cruzi, trypsanoma brucei brucei, and Crithidia fusiculata; as well as in schistosomiasis, malaria, tumor metastasis, metachromatic leukodystrophy, muscular dystrophy, amytrophy, and the like. See International Publication Number WO 94/04172, published on March 3, 1994, and references cited therein. See also International Publication Number WO 97/16433 , published on May 9, 1997, and references cited therein.

Pathological levels of cathepsin S have been implicated in a variety of disease states. For instance, mice treated with inhibitor exhibited attenuated antibody response indicating that selective inhibition of cathepsin S may provide a therapeutic strategy for asthma and autoimmune disease processes. Thus, selective inhibition of cathepsin S may provide an effective treatment for diseases requiring, for therapy or prevention: inhibition of a class II MHC-restricted immune response; treatment and/or prevention of an autoimmune disease state such as rheumatoid arthritis, multiple sclerosis, juvenile-onset diabetes, sytemic lupus erythematosus, discoid lupus erythematosus, pemphigus vulgaris, pemphigoid, Grave's disease, myasthenia gravis, Hashimoto's thyroiditis, scleroderma, dermatomysositis, Addison's disease, pernicious anemia, primary myxoedema, thyrotoxicosis, autoimmune atrophic gastritis, stiff-

man syndrome, Goodpasture's syndrome, sympathetic opthalamia, phacogenic uveitis, autoimmune haemolytic anaemia, idiopathic thrombocytopenic purpura, idiopathic leucopenia, primary biliary cirrhosis, active chronic hepatitis, cryptogenic cirrhosis, ulcerative colitis, Sjogren's syndrome, and mixed connective tissue diease; inhibition of an asthmatic response; inhibition of an allergic response; inhibition of immune response against transplanted organ or tissue inhibition of elastase activity in atheroma; and treatment or prevention of a disease state caused by the formation of atherosclerotic lesions or complications arising therefrom.

We have now discovered that certain 4-amino-azepan-3-one compounds inhibit cathepsin S, and are useful in the treatment of diseases in which cathepsin S is implicated.

SUMMARY OF THE INVENTION

An object of this invention is the use of compounds of Formula I or II for inhibiting the activity of the protease inhibitors known as cathepsin S.

Another object of the present invention is to provide novel 4-amino-azepan-3-one carbonyl compounds of Formula II, as described below.

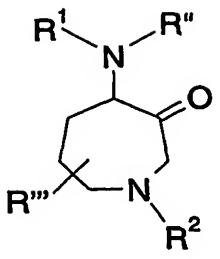
A further object of this invention is the use of a compound of Formula I or II in the manufacture of a medicament for treating or preventing a condition associated with the inhibition of cathepsin S.

Another aspect of this invention is that of a pharamceutical formulations comprising a compound of Formula II alone in admixture with a pharmaceutically acceptable excipient and administering this preparation to a mammal in need thereof in an amount effective for inhibiting cathepsin S to a degree which effects prevention of a condition or treatment of a condition associated with the inhibition of cathepsin S.

In a particular aspect, the methods of this invention are especially useful for treatment or prevention of autoimmune disease; treatment or prevention of a disease state caused by the formation of atherosclerotic lesions and complications arising therefrom; and diseases requiring inhibition, for therapy, of a class II MHC-restricted immune response, inhibition of an asthmatic response, inhibition of an allergic response, inhibition of immune response against a transplanted organ or tissue, or inhibition of elastase activity in atheroma.

DETAILED DESCRIPTION OF THE INVENTION

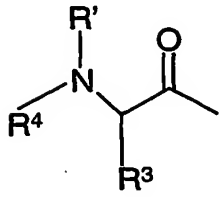
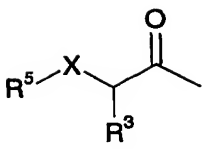
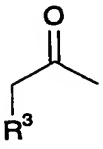
The present invention provides a method for treating a disease by inhibiting cathepsin S comprising administering at least one compound of Formula I neat or as a pharmaceutically acceptable formulation, in an effective amount, wherein Formula I comprises:



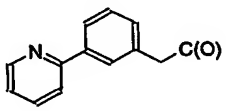
I

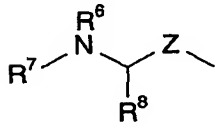
wherein:

R^1 is:


(a);

(b) or

(c);

R^2 is H, C_{1-6}alkyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, Ar-C_{0-6}alkyl, Het-C_{0-6}alkyl, $R^9C(O)$-, $R^9C(S)$-, R^9SO_2-, $R^9OC(O)$-,

$R^9R^{11}NC(O)$-, $R^9R^{11}NC(S)$-, $R^9(R^{11})NSO_2$-  or



R^3 is H or substituted or unsubstituted C_{1-6}alkyl, C_{3-7}cycloalkylC_{0-6}alkyl, C_{4-7}cycloalkenylC_{0-6}alkyl, C_{5-8}bicycloalkylC_{0-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, HetC_{0-6}alkyl, ArC_{0-6}alkyl, Ar-ArC_{0-6}alkyl, Ar-HetC_{0-6}alkyl, Het-ArC_{0-6}alkyl, or Het-HetC_{0-6}alkyl;

R^3 and R' may be connected to form a pyrrolidine, piperidine or morpholine ring;

R^4 is H, C_{1-6}alkyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, Ar-C_{0-6}alkyl, Het-C_{0-6}alkyl, $R^5C(O)$-, $R^5C(S)$-, R^5SO_2-, R^5NSO_2-, $R^5OC(O)$-, $R^5R^{13}NC(O)$-, or $R^5R^{13}NC(S)$-;

R^5 is H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, Ar-C_{0-6}alkyl, Ar-ArC_{0-6}alkyl, Ar-HetC_{0-6}alkyl, Het-ArC_{0-6}alkyl, Het-HetC_{0-6}alkyl, or Het-C_{0-6}alkyl;

R^6 is H, C_{1-6}alkyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, Ar-C_{0-6}alkyl, or Het-C_{0-6}alkyl;

R^7 is H, C_{1-6}alkyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, Ar-C_{0-6}alkyl, Het-C_{0-6}alkyl, $R^{10}C(O)$-, $R^{10}C(S)$-, $R^{10}SO_2$-, $R^{10}OC(O)$-, $R^{10}R^{14}NC(O)$-, or $R^{10}R^{14}NC(S)$-;

R^8 is H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, HetC_{0-6}alkyl or ArC_{0-6}alkyl;

R^9 is C_{1-6}alkyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, Ar-C_{0-6}alkyl or Het-C_{0-6}alkyl;

R^{10} is C_{1-6}alkyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, Ar-C_{0-6}alkyl or Het-C_{0-6}alkyl;

R^{11} is H, C_{1-6}alkyl, Ar-C_{0-6}alkyl, or Het-C_{0-6}alkyl;

R^{12} is H, C_{1-6}alkyl, Ar-C_{0-6}alkyl, or Het-C_{0-6}alkyl;

R^{13} is H, C_{1-6}alkyl, Ar-C_{0-6}alkyl, or Het-C_{0-6}alkyl;

R^{14} is H, C_{1-6}alkyl, Ar-C_{0-6}alkyl, or Het-C_{0-6}alkyl;

R' is H, C_{1-6}alkyl, Ar-C_{0-6}alkyl, or Het-C_{0-6}alkyl;

R" is H, C_{1-6}alkyl, Ar-C_{0-6}alkyl, or Het-C_{0-6}alkyl;

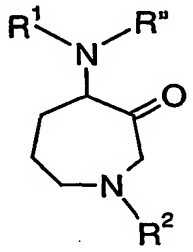
R"' is H, C_{1-6}alkyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, Ar-C_{0-6}alkyl, or Het-C_{0-6}alkyl;

X is CH_2, S, or O;

Z is C(O) or CH_2; or

a pharmaceutically acceptable salt, hydrate or solvate thereof.

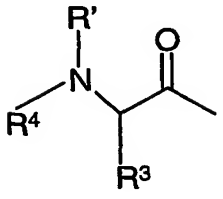
This invention further provides the compounds of Formula II:



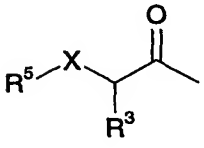
II

wherein:

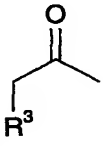
R^1 is:



(a);

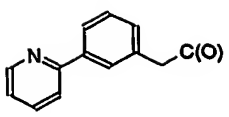
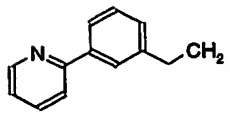
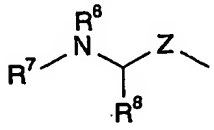


(b) or



(c);

R^2 is H, C_{1-6}alkyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, Ar-C_{0-6}alkyl, Het-C_{0-6}alkyl, $R^9C(O)$-, $R^9C(S)$-, R^9SO_2-, $R^9OC(O)$-,

$R^9R^{11}NC(O)$-, $R^9R^{11}NC(S)$-, $R^9(R^{11})NSO_2$-  ,  of  ;

R^3 is H or substituted or unsubstituted C_{1-6}alkyl, C_{3-7}cycloalkylC_{0-6}alkyl, C_{4-7}cycloalkenylC_{0-6}alkyl, C_{5-8}bicycloalkylC_{0-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, HetC_{0-6}alkyl, ArC_{0-6}alkyl, Ar-ArC_{0-6}alkyl, Ar-HetC_{0-6}alkyl, Het-ArC_{0-6}alkyl, or Het-HetC_{0-6}alkyl;

R^4 is H, C_{1-6}alkyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, Ar-C_{0-6}alkyl, Het-C_{0-6}alkyl, $R^5C(O)$-, $R^5C(S)$-, R^5SO_2-, R^5NSO_2-, $R^5OC(O)$-, $R^5R^{12}NC(O)$-, or $R^5R^{12}NC(S)$-;

R^5 is H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, Ar-C_{0-6}alkyl, Ar-ArC_{0-6}alkyl, Ar-HetC_{0-6}alkyl, Het-ArC_{0-6}alkyl, Het-HetC_{0-6}alkyl, or Het-C_{0-6}alkyl;

R^6 is H, C_{1-6}alkyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, Ar-C_{0-6}alkyl, or Het-C_{0-6}alkyl;

R^7 is H, C_{1-6}alkyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, Ar-C_{0-6}alkyl, Het-C_{0-6}alkyl, $R^{10}C(O)$-, $R^{10}C(S)$-, $R^{10}SO_2$-, $R^{10}OC(O)$-, $R^{10}R^{13}NC(O)$-, or $R^{10}R^{13}NC(S)$-;

R^8 is H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, HetC_{0-6}alkyl or ArC_{0-6}alkyl;

R^9 is C_{1-6}alkyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, Ar-C_{0-6}alkyl or Het-C_{0-6}alkyl;

R^{10} is C_{1-6}alkyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, Ar-C_{0-6}alkyl or Het-C_{0-6}alkyl;

R^{11} is H, C_{1-6}alkyl, Ar-C_{0-6}alkyl, or Het-C_{0-6}alkyl;

R^{12} is H, C_{1-6}alkyl, Ar-C_{0-6}alkyl, or Het-C_{0-6}alkyl;

R^{13} is H, C_{1-6}alkyl, Ar-C_{0-6}alkyl, or Het-C_{0-6}alkyl;

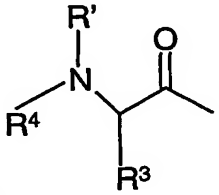
R' is H, C_{1-6}alkyl, Ar-C_{0-6}alkyl, or Het-C_{0-6}alkyl;

R" is C_{1-6}alkyl, Ar-C_{0-6}alkyl, or Het-C_{0-6}alkyl;

X is CH_2, S, or O;

Z is C(O) or CH_2; or

a pharmaceutically acceptable salt, hydrate or solvate thereof.



In compounds of Formula I or II, R^1 is preferably group (a) wherein:

R^3 is preferably substituted or unsubstituted C_{3-7}cycloalkylC_{0-6}alkyl, C_{4-7}cycloalkenylC_{0-6}alkyl, C_{5-8}bicycloalkylC_{0-6}alkyl, Ar-ArC_{0-6}alkyl, Ar-HetC_{0-6}alkyl, Het-ArC_{0-6}alkyl, or Het-HetC_{0-6}alky.

More preferably R^3 is substituted or unsubstituted C_{5-7}cycloalkylC_{1-2}alkyl, C_{4-5}cycloalkenylC_{1-2}alkyl, C_{5-8}bicycloalkylC_{1-2}alkyl or Ar-HetC_{0-6}alkyl.

Most preferably R^3 is cyclopentylmethyl, cyclopentylethyl, cyclopentenylmethyl, cyclopentenylethyl, cyclohexylmethyl, 4-methylcyclohexylmethyl, 2-cyclohexylprop-1-yl, cyclohexylethyl, cycloheptylmethyl, 7,7-dimethylbicyclo[2.2.1]hept-1ylmethyl, or indol-2-ylmethyl;

R^4 is $R^5C(O)$- or R^5SO_2- wherein R^5 is C_{3-6}cycloalkyl-C_{0-6}alkyl, Ar-ArC_{0-6}alkyl, Ar-HetC_{0-6}alkyl, Het-ArC_{0-6}alkyl, or Het-HetC_{0-6}alkyl.

More preferably R^5 is:

unsubstituted or substituted furanyl, especially furan-2-yl or furan-3-yl, or alkyl-substituted furanyl such as 2-methylfuran-3-yl, 2,4-dimethylfuran-3-yl, or aryl substituted furanyl, even more especially 5-phenylfuran-2-yl, 5-(2-chlorophenyl)furan-2-yl, 5-(3-chlorophenyl)furan-2-yl, 5-(4-chlorophenyl)furan-2-yl, 5-(4-fluorophenyl)furan-2-yl, 5-(4-hydroxyphenyl)furan-2-yl, 5-(3-trifluoromethylphenyl)furan-2-yl, 5-(4-trifluoromethylphenyl)furan-2-yl, 5-(3-trifluoromethylphenyl)furan-2-yl, 5-(4-methylphenyl)furan-2-yl, 5-(4-acetylphenyl)furan-2-yl, or 5-trifluoromethylfuran-2-yl;

unsubstituted or substituted tetrahydrofuranyl, particularly tetrahydrofuran-2-yl or tetrahydrofuran-3-yl

unsubstituted or substituted morpholinyl;

unsubstitutetd or substituted pyrrolyl, particularly pyrrol-2-yl;

unsubstituted or substituted piperazinyl, particularly piperzin-1-yl or 4-alkylpiperazinyl, e.g., 4-methylpeperzin-1-yl;

unsubstituted or substituted pyrazolyl, particularly 1H-pyrazol-2-yl, 1H-pyrazol-4-yl, 1- or 2-methyl-2H-pyrazol-2-yl or 1- or 2-methyl-2H-pyrazol-3-yl;

unsubstituted or substituted isoxazolyl, particularly isoxazol-5-yl, 3-methylisoxazol-4-yl, 5-methylisoxazol-3-yl, 5-methylisoxazol-4-yl, or 3,5-dimethylisoxazol-4-yl;

unsubstituted or substituted thiazolyl, particularly thiazol-2-yl, 2-methylthiazol-2-yl, 2,4-dimethylthiazol-5-yl, 2-(2,3-dihydrobenzo[1,4]dioxin-2-yl)thiazol-4-yl, or 4-methyl-2-phenylthiazol-5-yl;

unsubsituted or C_{1-2}alkylsubstituted pyrazolo[5,1-c]triazinyl, particularly 4,7-dimethylpyrazolo[5,1-c]triazin-3-yl;

unsubstituted or substituted pyrazolyl, particularly alkyl-substituted pyrazolyl including 2-methyl-2H-pyrazol-2-yl;

C_{1-2}alkyl substituted pyrazolo[5,1-c]pyrimidinyl, particularly 2,7-dimethylpyrazol[5,1-c]pyrimidin-6-yl;

unsubstituted or aryl-substituted triazolyl, particularly phenyl-substituted triazoles including 3-phenyl-3H-{1,2,3]triazol-3-yl;

unsubstituted or substituted pyrazinyl, particularly pyrazin-2-yl and 5-methylpyrazin-2-yl;

unsubstituted or substituted imadazolyl, particularly 1-H-imidazol-2-yl, 1-methyl-1H-imidazol-4-yl or 1-methyl-1H-imidazol-2-yl;

benzofuranyl, especially benzofuran-2-yl, more especially C_{1-6}alkoxy substituted benzofuranyl, particularly 5,6-dimethoxybenzofuran-2-yl, more especially Het-C_{0-6}alkyl-benzofuran-2-yl, particularly 5-(2-morpholin-4-yl-ethoxy)benzofuran-2-yl;

thiophenyl, especially thiophene-3-yl and thiophen-2-yl, more especially Het-C_{0-6}alkylthiophenyl; particularly 5-pyridin-2-ylthiophen-2-yl, more especially C_{1-6}alkylthiophenyl, particularly 5-methylthiophen-yl or 3-methylthiophen-2-yl; more especially C_{1-6}alkoxythiophenyl, particularly 3-ethoxythiophen-2-yl;

furo[3,2-b]-pyridine-2-yl, especially 3-methylfuro[3,2-b]pyridin-2-yl;

phenyl, especially alkyl-substituted phenyl, halogen-substitutedphenyl, trihaloalkyl-substituted phenyl, alkoxy-substituted phenyl, or acetoxy-substitutedphenyl, especially 4-methylphenyl, 3-chlorophenyl, 4-chlorophenyl, 3-trifluoromethylphenyl, 4-trifluoromethylphenyl, 2-chlorophenyl, 4-fluorophenyl, 4-hydroxyphenyl, or 4-acetylphenyl;

unsubstituted or substituted pyridinyl, particularly pyridin-2-yl;

cyclobutyl or cyclopentyl;

unsubstituted or substituted, for example thieno[3,2-b]thiopheneyl, especially thieno[3,2-b]thiophen-2-yl or 5-isoxazol-3-ylthiophen-2-yl.

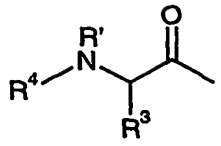
In group (a) R' is preferably H, C_{1-6}alkyl, Ar-C_{0-6}alkyl, or Het-C_{0-6}alkyl, preferably H.

In compounds of Formula I and II, R^2 is preferably R^9SO_2 or C_{1-6}alkyl. When R^2 is C_{1-6}alkyl, C_{1-6}alkyl is preferably propyl. R^2 is most preferably R^9SO_2.

R^9 is C_{1-6}alkyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, Ar-C_{0-6}alkyl, or Het-C_{0-6}alkyl, preferably Het-C_{0-6}alkyl, more preferably pyridinyl or 1-oxy-pyridinyl. When R^2 is R^9SO_2, R^9 is even more preferably pyridin-2-yl or 1-oxy-pyridin-2-yl. Most preferably, R^9 is pyridin-2-yl.

Most preferred compounds of Formula I or II are those wherein:

R^1 is group (a)



;

R^2 is R^9SO_2;

R^3 is cyclopentylmethyl, cyclopentylethyl, cyclopentenylmethyl, cyclopentenylethyl, cyclohexylmethyl, 4-methylcyclohexylmethyl, 2-cyclohexylprop-1-yl, cyclohexylethyl, cycloheptylmethyl, 7,7-dimethylbicyclo[2.2.1]hept-1ylmethyl, or indol-2-ylmethyl;

R^4 is $R^5C(O)$ or R^5SO_2;

R^5 is 5-phenylfuran-2-yl, 5-(2-chlorophenyl)furan-2-yl, 5-(3-chlorophenyl)furan-2-yl, 5-(4-chlorophenyl)furan-2-yl, 5-(4-fluorophenyl)furan-2-yl, 5-(4-hydroxyphenyl)furan-2-yl, 5-(3-trifluoromethylphenyl)furan-2-yl, 5-(4-trifluoromethylphenyl)furan-2-yl, 5-(3-trifluoromethylphenyl)furan-2-yl, 5-(4-methylphenyl)furan-2-yl, 5-(4-acetylphenyl)furan-2-yl, or 5-trifluoromethylfuran-2-yl;

tetrahydrofuran-2-yl or tetrahydrofuran-3-yl

N-morpholinyl;

pyrrol-2-yl

piperzin-1-yl or 4-alkylpiperazinyl, e.g., 4-methylpeperzin-1-yl;

1H-pyrazol-2-yl, 1H-pyrazol-4-yl, 1- or 2-methyl-2H-pyrazol-2-yl or 1- or 2-methyl-2H-pyrazol-3-yl;

isoxazol-5-yl, 3-methylisoxazol-4-yl, 5-methylisoxazol-3-yl, 5-methylisoxazol-4-yl, or 3,5-dimethylisoxazol-4-yl;

thiazol-2-yl, 2-methylthiazol-2-yl, 2,4-dimethylthiazol-5-yl, 2-(2,3-dihydrobenzo[1,4]dioxin-2-yl)thiazol-4-yl, or 4-methyl-2-phenylthiazol-5-yl;

4,7-dimethylpyrazolo[5,1-c]triazin-3-yl;

2-methyl-2H-pyrazol-2-yl;

2,7-dimethylpyrazol[5,1-c]pyrimidin-6-yl;

3-phenyl-3H-{1,2,3]triazol-3-yl;

pyrazin-2-yl or 5-methylpyrazin-2-yl;

1-H-imidazol-2-yl, 1-methyl-1H-imidazol-4-yl or 1-methyl-1H-imidazol-2-yl;

benzofuran-2-yl, 5,6-dimethoxybenzofuran-2-yl, 5-(2-morpholin-4-yl-ethoxy)benzofuran-2-yl;

thiophene-3-yl, thiophen-2-yl, 5-pyridin-2-ylthiophen-2-yl, 5-methylthiophen-yl or 3-methylthiophen-2-yl, or 3-ethoxythiophen-2-yl;

furo[3,2-b]-pyridine-2-yl or 3-methylfuro[3,2-b]pyridin-2-yl;

phenyl, 4-methylphenyl, 3-chlorophenyl, 4-chlorophenyl, 3-trifluoromethylphenyl, 4-trifluoromethylphenyl, 2-chlorophenyl, 4-fluorophenyl, 4-hydroxyphenyl, or 4-acetylphenyl;

pyridin-2-yl;

thieno[3,2-b]thiophen-2-yl or 5-isoxazol-3-ylthiophen-2-yl

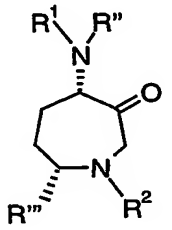
R^9 is pyridin-2-yl or 1-oxy-pyridin-2-yl, preferably pyridin-2-yl;

R' is H

R" is H; and

in Formula I R''' is C_{1-6}alkyl.

R''' is preferably methyl, ethyl, propyl, butyl, pentyl and hexyl, more especially methyl; or preferably 5-, 6- or 7- C_{1-6}alkyl, especially 5-, 6- or 7-methyl, -ethyl, -propyl, -butyl, -pentyl or -hexyl, more especially 5-, 6- or 7-methyl; more preferably 6- or 7- C_{1-6}alkyl, especially 6- or 7-methyl, -ethyl, -propyl, -butyl, -pentyl and -hexyl, more especially 6- or 7-methyl; yet more preferably, in Formula I, *cis*-7- C_{1-6}alkyl as shown in Formula Ia:



Ia

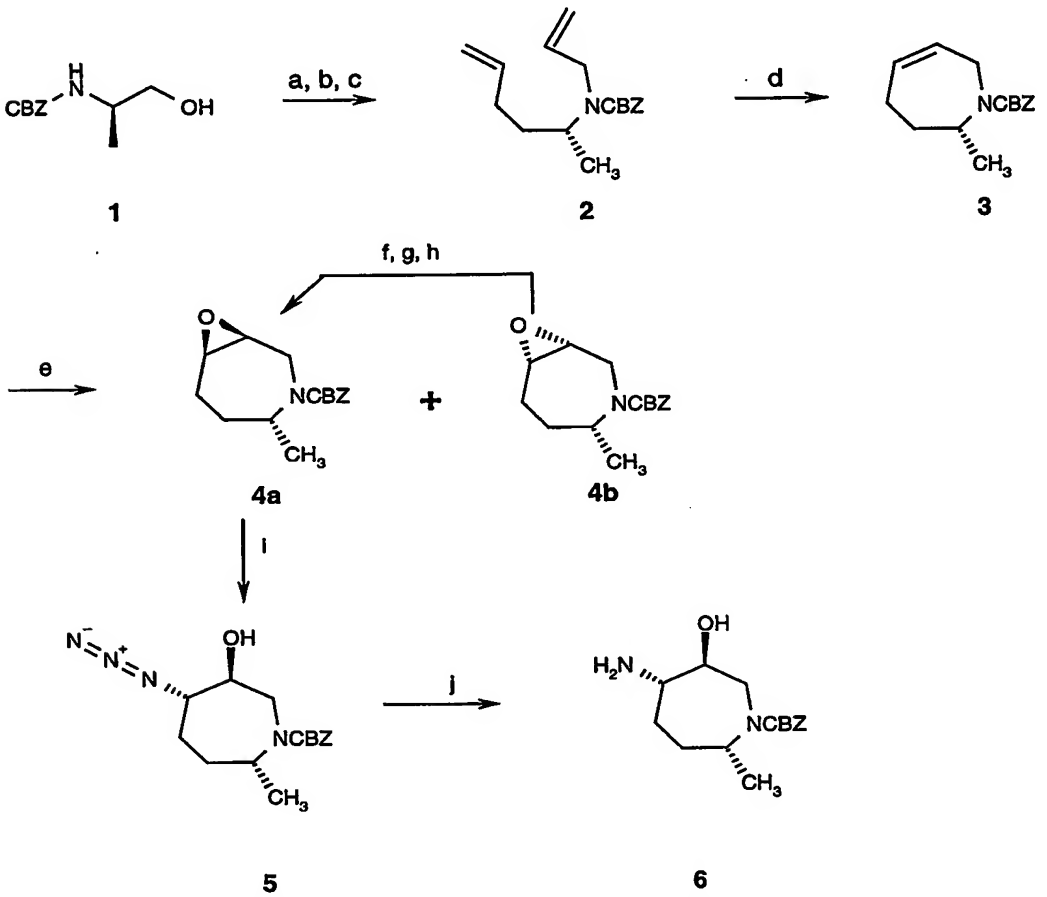
wherein R''' is C_{1-6}alkyl, especially selected from the group consisting of: methyl, ethyl, propyl, butyl, pentyl and hexyl; most preferably *cis*-7- methyl, as shown in Formula Ia wherein R''' is methyl.

As for the preferred substituents of Formula II, the definition are the same as those of the preferred compounds of Formula I with the exception of R^3. For it the preferred groups are cyclopentylmethyl, [1-methylcyclopentyl]methyl, cyclopentylethyl, cyclopent-1-enylmethyl, cyclohexylmethyl, cycloheptylmethyl, [4-methylyclohexyl]methyl, [1-methylyclohexyl]methyl, and [2-7,7-dimethylbicyclo[2.2.1]hept-1-yl]ethyl. These preferred compounds, in particular, as well as other compounds of Formula II, are highly selective for inhibition of the cathepsin S enzyme as compared with their inhibition of the cathepsin K enzyme. Expressed as the ratio of the K_i for cathepsin K over the K_i of cathepsin S, (K_i Cat K/K_i Cat S) these novel compounds exhibit a ratio of 4 or greater in (define assay). The assay is described below.

Methods of Preparation

Compounds of the general formula Ia may be prepared in a fashion analogous to that outlined in Schemes 1 to 7. Carbobenyzloxy-D-alaninol (Cbz-D-alaninol)1 is first converted into an iodide and is then reacted with allyl Grignard with a copper (I) catalyst or a similar allyl organometallic reagent. The amine is then alkylated with allyl iodide. Grubbs' catalyst is then used to form the azepine ring 3 by ring closing metathesis. Epoxidation of the alkene followed by separation of the diastereomers and opening of the epoxide of the minor component with sodium azide provides the intermediate azido alcohol 5. Reduction of the azide 5 produces amine 6.

Scheme 1

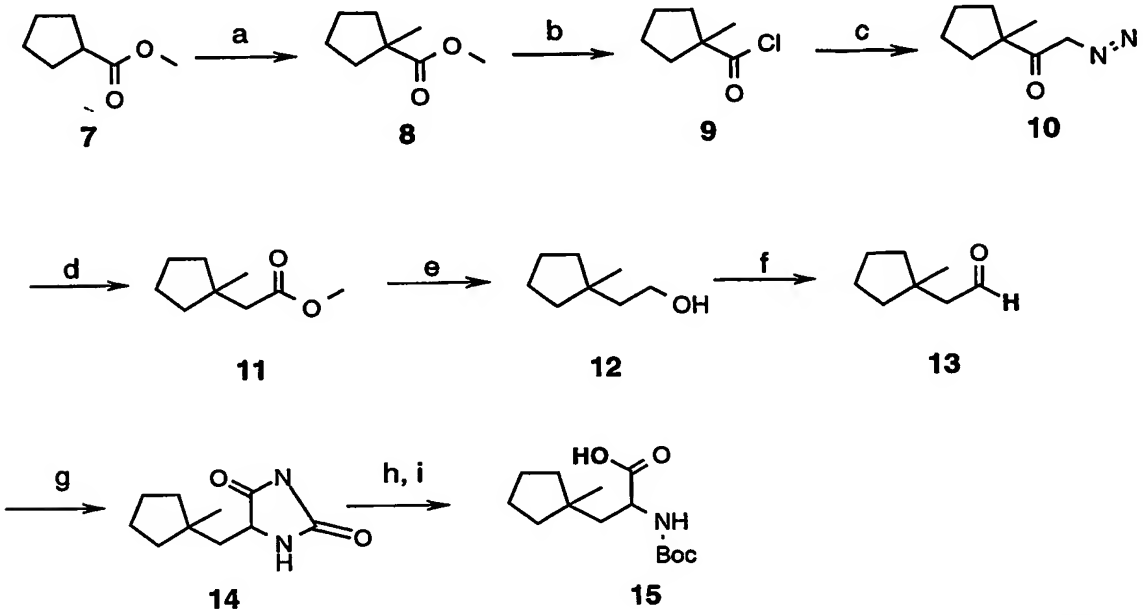


Reagents and conditions: (a) PPh_3, I_2; (b) 2-propenyl magnesium chloride, Cat. CuI; (c) allyl bromide, NaH; (d) Grubbs; (e) mCPBA; f) KOAc/ HOAc, 18-crown-6; g) $MeSO_2Cl$, Et_3N; h) KOH, MeOH; i) NaN_3; j) PPh_3

Commercially available methyl cyclopentane carboxylate was methylated with LDA and iodomethane to give 8 (scheme 2) Hydrolysis of the ester with LiOH followed by treatment with oxalyl chloride gives acid chloride 9. Subsequent Wolff rearrangement with

diazomethane and silver benzoate produces ester 11. Reduction of the ester followed by oxidition with Dess-Martin periodinane produces aldehyde 13. This in turn is treated with KCN and $(NH_4)CO_3$ followed by hydrolysis with NaOH and protection of the free amine as its BOC carbamate to give amino acid 15.

Scheme 2

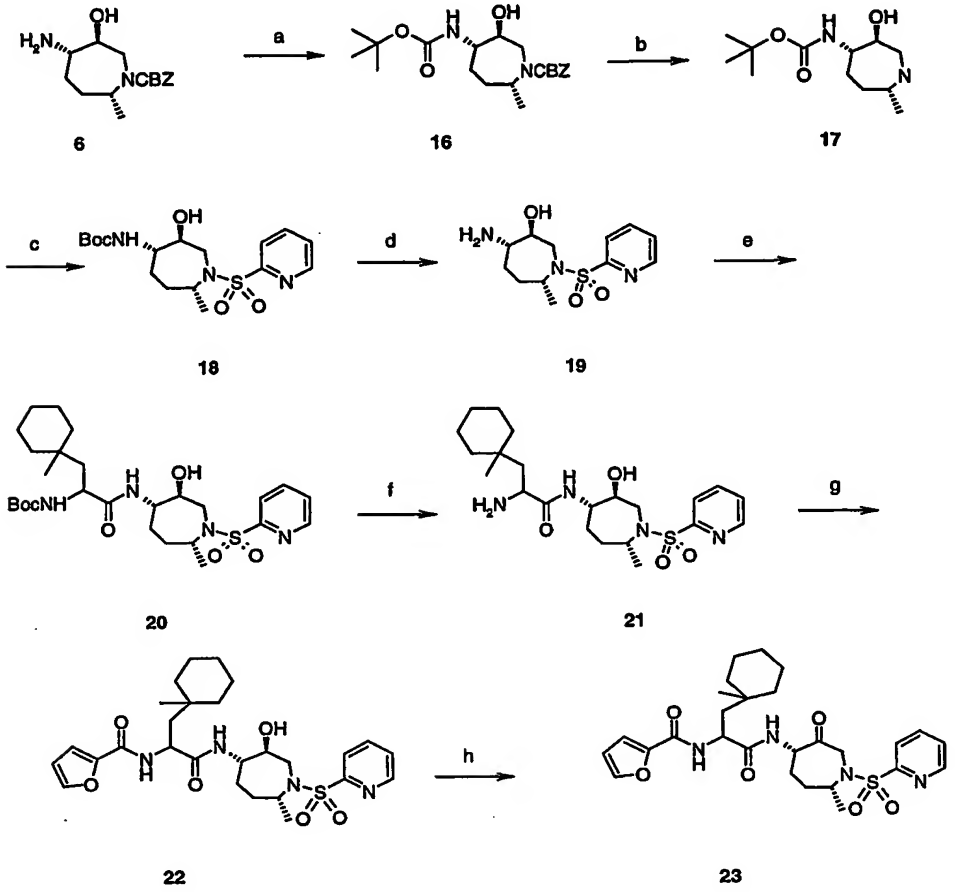


Reagents and conditions: (a) BuLi, diisopropylamine, MeI; b) LiOH, oxalylchloride; (c) CH_2N_2, Et_3N; (d) silver benzoate, Et_3N, MeOH; (e) $LiAlH_4$; f) Dess- Martin; g) KCN, $(NH_4)_2CO_3$, HCl; h) NaOH; i) $(Boc)_2O$.

The amine 6 may be protected with di-*tert*-butyldicarbonate to provide the N-Boc derivative 16 (Scheme 3). Removal of the benzyloxycarbonyl protecting group may be effected by treatment of 16 with hydrogen gas in the presence of a catalyst such as 10% Pd/C to provide the amine 17. Treatment of amine 17 with a sulfonyl chloride such as 2-pyridinesulfonyl chloride in the presence of a base such as N-methylmorpholine or triethylamine provides the sulfonamide derivative 18. Removal of the *tert*-butoxycarbonyl protecting group may be effected with an acid such as hydrochloric acid to provide intermediate 19. Coupling of 19 with an acid such as N-Boc-(1-methyl)cyclohexylalanine in the presence of a coupling agent common to the art such as HBTU or polymer supported EDC provides the alcohol intermediate 20. Removal of the *tert*-butoxycarbonyl protecting group under acidic conditions provides amine 21. Coupling of 21 with an acid such as furan-2-carboxylic acid in the presence of a coupling agent such as HBTU or polymer supported EDC provides alcohol 22. Alcohol 22 may be oxidized with an oxidant common to the art such as

pyridine sulfur trioxide complex in DMSO and triethylamine or the Dess-Martin periodinane to provide the ketone 23.

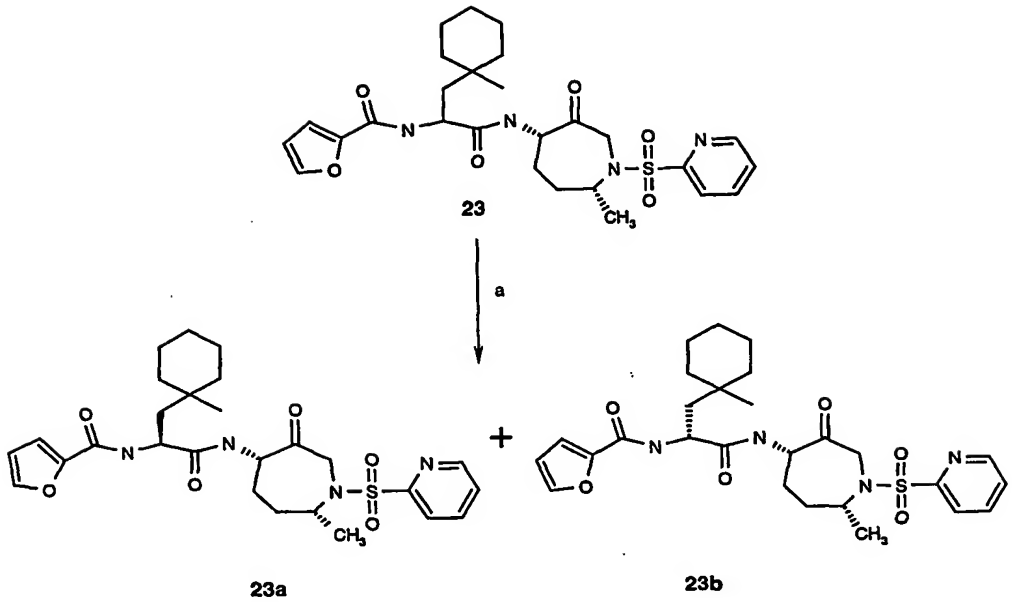
Scheme 3



Reagents and conditions: (a) Di-*tert*-butyldicarbonate, THF; (b) H_2, 10% Pd/C, EtOAc; (c) 2- pyridinesulfonyl chloride, TEA, DMF; (d) HCl, MeOH; (e) N-Boc-1-methylcylohexylalanine, HBTU, 4-methylmorpholine, DMF; (f) HCl, MeOH; (g) furan-2-carboxylic acid, HBTU, 4-methylmorpholine, DMF; (h) Dess-Martin periodinane, methylene chloride.

The individual diastereomers of furan-2-carboxylic acid {(S)-2-[1-methylcyclohexyl-1-(4S,7R)-7-methyl-3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide 23a and 23b may be prepared as outlined in Scheme 4. The mixture of diastereomers are separated by HPLC to provide the compounds 23a and 23b.

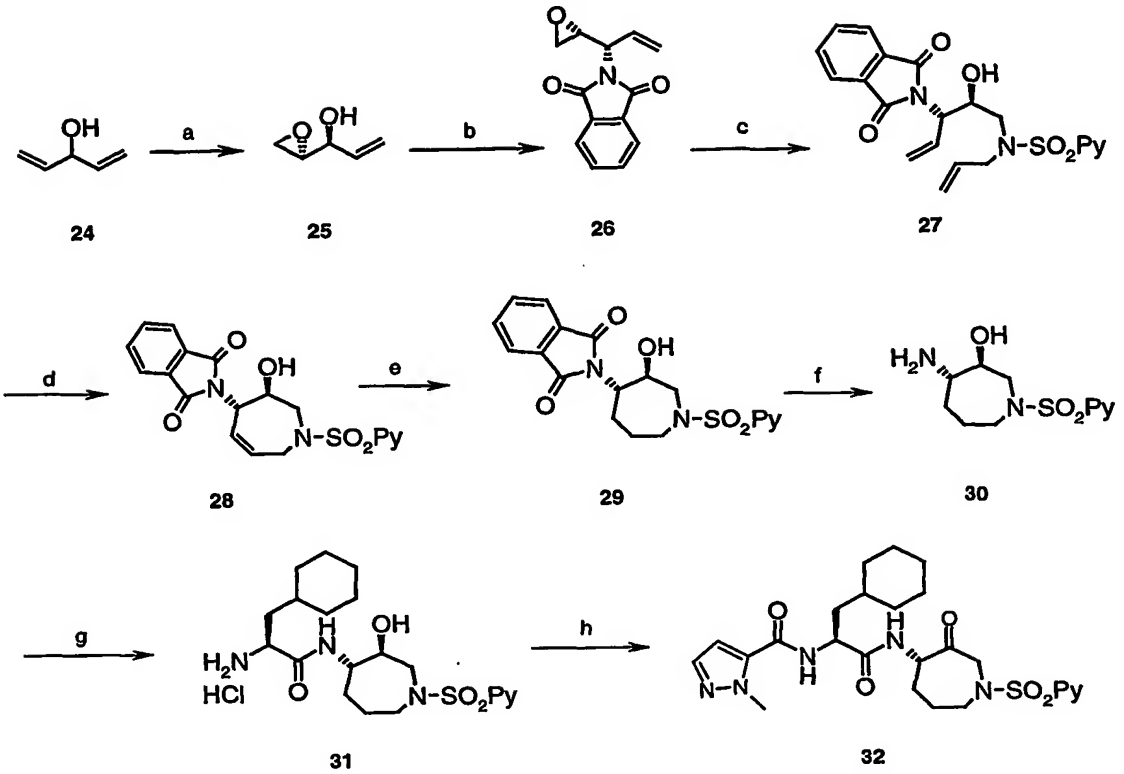
Scheme 4



Reagents and Conditions: a.) HPLC separation.

Alternatively, the compounds of formula 1a may be prepared in a fashion analogous to Scheme 5. Thus, 1,4-pentadien-3-ol was epoxidized under Sharpless epoxidation conditions using cumene hydroperoxide and D-(-)-diisopropyl tartrate. The resulting secondary alcohol was inverted under Mitsonobu conditions with phthalimide to reveal epoxide 26. Opening of this epoxide with pyridine-2-sulfonic acid allylamide in the presence of DBU and subsequent ring-closing metathesis with Grubb's catalyst provided alkene 28. The olefin was hydrogenated over palladium on carbon and the phthalimide protecting group removed with hydrazine to reveal amine 30. The amine can then be used to couple to (S)-2-tert-Butoxycarbonylamino-3-cyclohexyl-propionic acid to provide intermediate 31. Subsequent removal of the tert-butoxycarbonyl protecting group, coupling with a carboxylic acid, and oxidation of the C3 secondary alcohol to the ketone provided 32.

Scheme 5

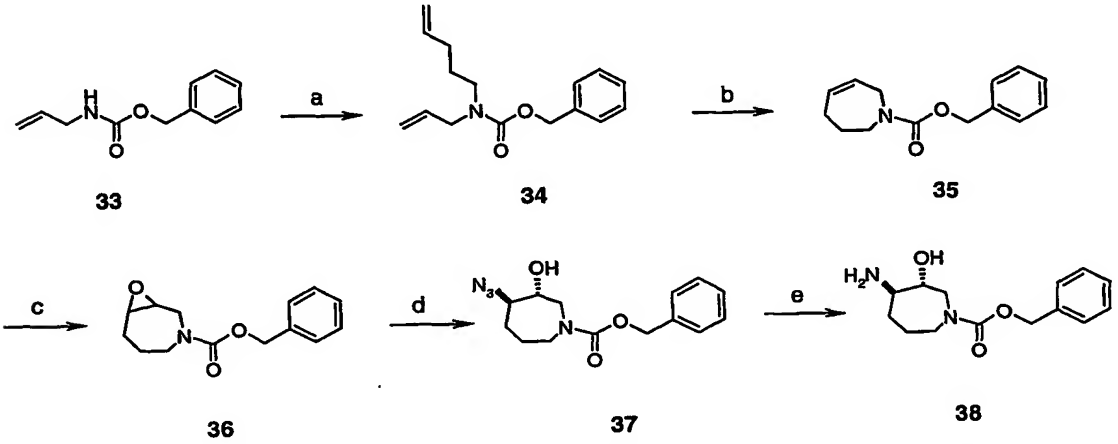


Reagents and conditions: a) $Ti(OiPr)_4$, cumene hydroperoxide, 4A molecular sieves, D-(-)-DIPT; b) phthalimide, Ph_3P,DIAD; c) Pyridine-2-sulfonic acid allylamide, DBU; d) Tricyclohexylphosphine (1,3-bistrimethylphenyl 4,5-dihydroimidazol-2-ylidene) benzylidene ruthenium (IV) dichloride; e) H_2(g), Pd/C, 45°C; f) NH_2NH_2, MeOH, reflux; g) i) (S)-2-tert-butoxycarbonylamino-3-cyclohexyl-propionic acid, HBTU, 4-methylmorpholine; ii) 4N HCl; h) i) 2-methyl-2H-pyrazole-3-carboxylic acid, HBTU, 4-methylmorpholine; ii) Dess-Martin Periodinane

Compounds of the general formula Ia may also be prepared in a fashion analogous to that outlined in Schemes 6 to 7. Alkylation of benzyl-N-allylcarbamate (**33**) with a base such as sodium hydride and 5-bromo-1-pentene provides the diene **34** (Scheme 1). Treatment of **2** bis(tricyclohexylphosphine)benzylidine ruthenium (IV) dichloride olefin metathesis catalysts developed by Grubbs provides the tetrahydroazepine **35**. Epoxidation of **35** with oxidizing agents common to the art such as *m*-CPBA provides the epoxide **36**. Nucleophilic epoxide ring opening may be effected with a reagent such as sodium azide to provide the azido alcohol **37** which may be reduced to the amino alcohol **38** under conditions common to the art such as 1,3-propanedithiol and triethylamine in methanol or triphenylphosphine in THF and water. Treatment of amine **38** with S-Boc-cyclopentyl alanine in the presence of HBTU and 4-

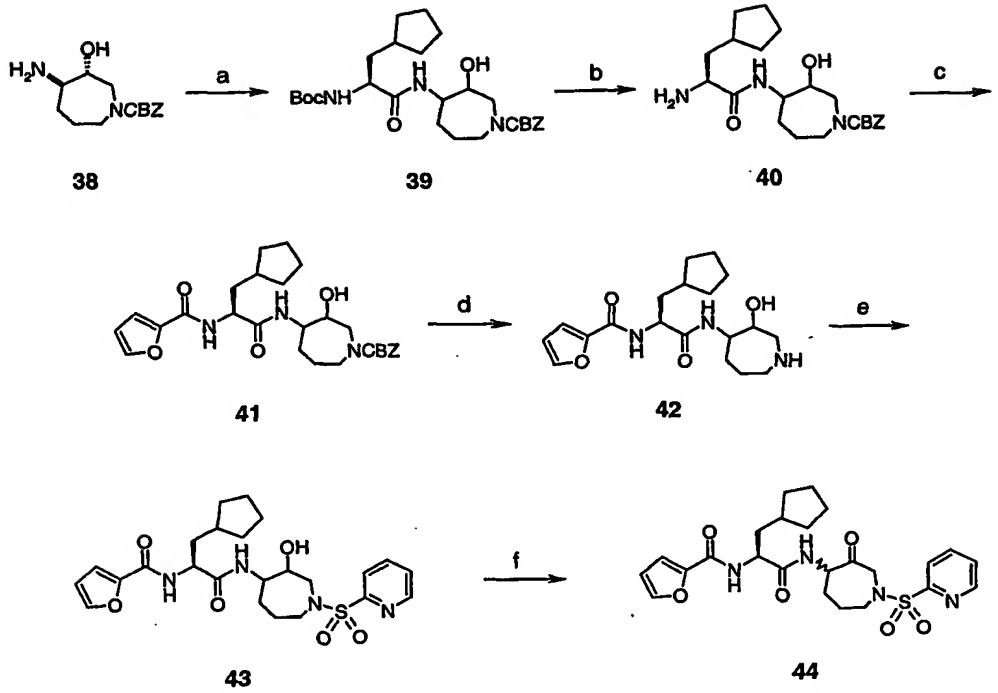
methylmorpholine affords compound **39**. Removal of the tert-butoxycarbonyl protecting group may be effected by treatment of **39** with hydrogen chloride in dioxane to produce the amine **40**. Treatment of amine **40** with 2-furoic acid in the presence of HBTU and 4-methylmorpholine produces compound **41**. The benzyloxycarbonyl protecting group may be removed by treatment with TMSI in methylene chloride to provide amine **42**. Treatment of amine **42** with a sulfonyl chloride such as 2-pyridinesulfonyl chloride in the presence of a base such as sodium bicarbonate gives secondary alcohol **43**. Alcohol **43** may be oxidized with an oxidant common to the art such as pyridine sulfur trioxide complex in DMSO and triethylamine or the Dess-Martin periodinane to provide the ketone **44**.

Scheme 6



Reagents and conditions: (a) NaH, 5-bromo-1-pentene, NaH; (b) bis(tricyclohexyl-phosphine)benzylidine ruthenium (IV) dichloride, CH_2Cl_2, reflux; (c) *m*-CPBA, CH_2Cl_2; (d) NaN_3, NH_4Cl, CH_3OH, H_2O; (e) TEA, 1,3-propanedithiol, CH_3OH.

Scheme 7



Reagents and conditions: (a) N-Boc-cylcopentylalanine, HBTU, 4-methylmorpholine, DMF; (b) HCl, dioxane; (c) 2-furoic acid, HBTU, 4-methylmorpholine, DMF; (d) TMSI, CH_2Cl_2; (e) 2-pyridyl sulfonylchloride, 10% sodium bicarbonate; (f) Dess-Martin periodinane, methylene chloride.

Utility of the Present Invention

The compounds of Formula I and II are useful as inhibitors of cathepsin S. The present invention provides methods of treatment of diseases caused by pathological levels of cathepsin S, which methods comprise administering to an animal, particularly a mammal, most particularly a human in need thereof a therapeutically effective amount of an inhibitor of cathepsin S, including a compound of the present invention.

The present invention particularly provides methods for treating the following diseases in which cathepsin S is implicated:

treatment and/or prevention of an autoimmune disease state such as rheumatoid arthritis, multiple sclerosis, juvenile-onset diabetes, systemic lupus erythematosus, discoid lupus erythematosus, pemphigus vulgaris, pemphigoid, Grave's disease, myasthenia gravis, Hashimoto's thyroiditis, scleroderma, dermatomysositis, Addison's disease, pernicious anemia, primary myxoedema, thyrotoxicosis, autoimmune atrophic gastritis, stiff-man syndrome, Goodpasture's syndrome, sympathetic opthalamia, phacogenic uveitis, autoimmune haemolytic

anaemia, idiopathic thrombocytopenic purpura, idiopathic leucopenia, primary biliary cirrhosis, active chronic hepatitis, cryptogenic cirrhosis, ulcerative colitis, Sjogren's syndrome, and mixed connective tissue diease; and

treatment and/or prevention of a disease state caused by the formation and/or complications of atherosclerotic lesions.

Diseases which require therapy:

inhibition of a class II MHC-restricted immune response;

inhibition of an asthmatic response;

inhibition of an allergic response such as allergic rhinitis or atopic dermatitis;

inhibition of immune response against transplanted organ or tissue; and

inhibition of elastase activity in atheroma.

The present methods contemplate the use of one or more compounds of Formula I or II alone or in combination with other therapeutic agents.

For acute therapy, parenteral administration of a compound of Formula I or II is preferred. An intravenous infusion of the compound in 5% dextrose in water or normal saline, or a similar formulation with suitable excipients, is most effective, although an intramuscular bolus injection is also useful. Typically, the parenteral dose will be about 0.01 to about 100 mg/kg; preferably between 0.1 and 20 mg/kg, in a manner to maintain the concentration of drug in the plasma at a concentration effective to inhibit cathepsin S. The compounds are administered one to four times daily at a level to achieve a total daily dose of about 0.4 to about 400 mg/kg/day. The precise amount of a compound which is therapeutically effective, and the route by which such compound is best administered, is readily determined by one of ordinary skill in the art by comparing the blood level of the agent to the concentration required to have a therapeutic effect.

The compounds of Formula I or II may also be administered orally to the patient in a manner such that the concentration of drug is sufficient to inhibit bone resorption or to achieve any other therapeutic indication as disclosed herein. Typically, a pharmaceutical composition containing the compound is administered at an oral dose of between about 0.1 to about 50 mg/kg in a manner consistent with the condition of the patient. Preferably the oral dose would be about 0.5 to about 20 mg/kg.

No unacceptable toxicological effects are expected when compounds of Formula I or II are administered in accordance with the present methods.

Biological Assays

The compounds used in the present methods may be tested in one of several biological assays to determine the concentration of compound which is required to have a given pharmacological effect.

Determination of cathepsin S proteolytic catalytic activity

All assays for cathepsin S were carried out with human recombinant enzyme. Standard assay conditions for the determination of kinetic constants used a fluorogenic peptide substrate, typically Ac-Lys-Gln-Lys-Leu-Arg-AMC, and were determined in 50 mM Mes at pH 6.5 containing 10 mM cysteine and 5 mM EDTA. Stock substrate solutions were prepared at a concentration of 10 mM in 10 % DMSO with 30 uM final substrate concentration in the assays. All assays contained 6% DMSO. All assays were conducted at 30° C . Product fluorescence (excitation at 360 nM; emission at 460 nM) was monitored either with a Perceptive Biosystems Cytofluor II fluorescent plate reader or a Tecan Spectraflour Plus plate reader. Product progress curves were generated over 20 to 30 minutes following formation of AMC product.

Determination of cathepsin K proteolytic catalytic activity

All assays for cathepsin K were carried out with human recombinant enzyme. Standard assay conditions for the determination of kinetic constants used a fluorogenic peptide substrate, typically Cbz-Phe-Arg-AMC, and were determined in 100 mM Na acetate at pH 5.5 containing 20 mM cysteine and 5 mM EDTA. Stock substrate solutions were prepared at a concentration of 10 mM in DMSO with 20 uM final substrate concentration in the assays. All assays contained 10% DMSO. All assays were conducted at 30° C . Product fluorescence (excitation at 360 nM; emission at 460 nM) was monitored either with a Perceptive Biosystems Cytofluor II fluorescent plate reader or a Tecan Spectraflour Plus plate reader. Product progress curves were generated over 20 to 30 minutes following formation of AMC product.

Determination of cathepsin L proteolytic catalytic activity

All assays for cathepsin L were carried out with human liver cathepsin L purchased from Enzyme Systems Products. Standard assay conditions are the same as cathepsin K except that the final substrate concentration was 5.0 uM.

Inhibition studies

Potential inhibitors were evaluated using the progress curve method. Assays were carried out in the presence of variable concentrations of test compound. Reactions were initiated by addition of enzyme to buffered solutions of inhibitor and substrate. Data analysis was conducted according to one of two procedures depending on the appearance of the progress curves in the presence of inhibitors. For those compounds whose progress curves were linear, apparent inhibition constants ($K_{i,app}$) were calculated according to equation 1 (Brandt *et al.*, *Biochemitsry,* 1989, *28*, 140):

$$v = V_m A / [K_a(1 + I/K_{i,\,app}) + A] \qquad (1)$$

where v is the velocity of the reaction with maximal velocity V_m, A is the concentration of substrate with Michaelis constant of K_a, and I is the concentration of inhibitor.

For those compounds whose progress curves showed downward curvature characteristic of time-dependent inhibition, the data from individual sets was analyzed to give k_{obs} according to equation 2:

$$[AMC] = v_{ss}\, t + (v_0 - v_{ss})\,[1 - exp\,(-k_{obs}t)] / k_{obs} \qquad (2)$$

where [AMC] is the concentration of product formed over time t, v_0 is the initial reaction velocity and v_{ss} is the final steady state rate. Values for k_{obs} were then analyzed as a linear function of inhibitor concentration to generate an apparent second order rate constant (k_{obs} / inhibitor concentration or k_{obs}/ [I]) describing the time-dependent inhibition. A complete discussion of this kinetic treatment has been fully described (Morrison *et al.*, *Adv. Enzymol. Relat. Areas Mol. Biol.*, 1988, *61*, 201).

General

Nuclear magnetic resonance spectra were recorded at 400 MHz using, respectively, a Bruker AC 400 spectrometer. $CDCl_3$ is deuteriochloroform, DMSO-d_6 is hexadeuteriodimethylsulfoxide, and CD_3OD is tetradeuteriomethanol. Chemical shifts are reported in parts per million (δ) downfield from the internal standard tetramethylsilane. Abbreviations for NMR data are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, dt = doublet of triplets, app = apparent, br = broad. J indicates the NMR coupling constant measured in Hertz. Continuous wave infrared (IR) spectra were recorded on a Perkin-Elmer 683 infrared spectrometer, and Fourier transform

infrared (FTIR) spectra were recorded on a Nicolet Impact 400 D infrared spectrometer. IR and FTIR spectra were recorded in transmission mode, and band positions are reported in inverse wavenumbers (cm^{-1}). Mass spectra were taken on either VG 70 FE, PE Syx API III, or VG ZAB HF instruments, using fast atom bombardment (FAB) or electrospray (ES) ionization techniques. Elemental analyses were obtained using a Perkin-Elmer 240C elemental analyzer. Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. All temperatures are reported in degrees Celsius.

Analtech Silica Gel GF and E. Merck Silica Gel 60 F-254 thin layer plates were used for thin layer chromatography. Both flash and gravity chromatography were carried out on E. Merck Kieselgel 60 (230-400 mesh) silica gel.

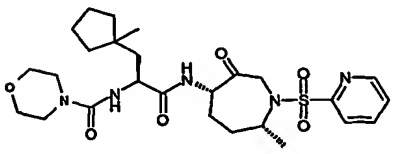
Where indicated, certain of the materials were purchased from the Aldrich Chemical Co., Milwaukee, Wisconsin, Chemical Dynamics Corp., South Plainfield, New Jersey, and Advanced Chemtech, Louisville, Kentucky.

Examples

In the following synthetic examples, temperature is in degrees Centigrade (°C). Unless otherwise indicated, all of the starting materials were obtained from commercial sources. Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. These Examples are given to illustrate the invention, not to limit its scope. Reference is made to the claims for what is reserved to the inventors hereunder.

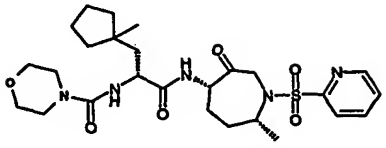
Example 1

Preparation of 1A: Morpholine 4-carboxylic acid {(S)-2-[1-methylcyclopentyl-1-(4S,7R)-7-methyl-3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide;



1A

Preparation of 1B: Morpholine 4-carboxylic acid {(L)-2-[1-methylcyclopentyl-1-(4S,7R)-7-methyl-3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide;



1B

1a.) 1-Methyl methylcyclopentanecarboxylate

Butyllithium (1.6 M, 48.75 mL, 78 mmol) was added dropwise to a stirred solution of diisopropylamine (7.88 g, 44.5 mmol) in tetrahydrofuran (12 mL) at –78°C. The solution was warmed to room temperature to ensure the evaporation of butane and then cooled to –78°C again. Methylcyclopentanecarboxylate (10.0 g, 78 mmol) in tetrahydrofuran (100 mL) was added to the reaction mixture at –78°C. After addition, the reaction mixture was warmed to 0°C temperature for 30 mins. After cooling to –78°C, iodomethane (11.1 g, 78 mmol) in tetrahydrofuran (30 mL) was added. After addition, the reaction mixture was warmed to room temperature and stirred for 18 hours. Ammonium chloride solution (saturated) was added and the suspension was extracted with ether (3x). The combined organic phase was washed with water, brine, dried ($MgSO_4$), filtered and concentrated. Column chromatography (5% ethyl acetate:hexanes) of the residue provided 5.3 g of the title compound: ^{1}HNMR: ($CDCL_3$) δ 3.7 (s, 3H), 2.10 (s, 3H), 1.28-1.70 (m, 8H).

1b.) 1-Methylcyclopentanecarboxlic acid

To a solution of compound of Example 1a (5.3 g) in methanol was added lithium hydroxide (15.68 g, 0.4 mol). The reaction was stirred at room temperature for 18 hours. The reaction was concentrated *in vacuo*. The solution was adjusted to pH=1 with 10% HCl solution, and extracted with ethyl acetate. The combined organic phase was washed with water, brine, dried ($MgSO_4$), filtered and concentrated to give 5.0 g of the title compound: ^{1}HNMR: ($CDCL_3$) δ 2.10 (s, 3H), 1.26-1.73 (m, 8H).

1c.) 1-Methyl cyclopentanecarbonyl chloride

To a solution of the compound of Example 1b (5.0 g, 38.5 mmol) and oxalylchloride (3.6 mL) in CH_2Cl_2, 0.2 mL of DMF was added. The mixture was stirred overnight at room temperature. The solvent was removed under reduced pressure to give 5.0 g (crude) of the title compound which was used directly in the next step without further purification.

1d.) 1-Diazomethyl-1-methyl-cyclopentane

Triethylamine (6.12 mL, 43.94 mmol) was added to a solution of the 1-methyl cyclopentanecarbonyl chloride from Example 1c (5.0 g, 33.8 mmol) and diazomethane (1.47 g,

35 mmol) in a mixture of CH_3CN (25 mL) and THF (25 mL) at 0°C. After the addition was complete, the reaction mixture was allowed to warm room temperature for 20 hours. The solvent was removed under reduced pressure and the resulting residue washed with $NaHCO_3$ (sat.) solution and was extracted with ether (3x). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated to provide 4.0 g of the title compound: IR: N=N 2112.29 (cm^{-1})

1e.) (1-Methyl-cyclopentyl)-acetic acid methyl ester

To a solution of the title compound of Example 1d (4.0 g, 25.8 mmol) in methanol (106 mL), 4mL of silver benzoate (1.07 g) in triethyl amine (13.8 mL) was added. After addition, the reaction mixture was stirred at room temperature for 2 hours whereupon it was filtered to remove the solids. The filtrate was evaporated *in vacuo*. Column chromatography of the residue (20% ethyl acetate:hexane) provided 1.8 g of the title compound: ^1H NMR: ($CDCl_3$) δ 3.70 (s, 3H), 2.27 (s, 2H), 2.02 (s, 3H), 1.21-1.60 (m, 8H).

1f.) (1-Methyl-cyclopentyl)-ethanol

To a stirring solution of lithium aluminum hydride (24.73 mL, 23 mmol) in THF, the title compound of Example 1e (1.8 g, 11.5 mmol) was added slowly. After the addition, the mixture was stirred at reflux temperature for 2 hours after which time it was cooled to 0°C. Benzene (45 mL), water (1.77 mL) (added very slowly) and sodium fluoride (3.14 g) were added and stirred at 0°C for 1 hour whereupon the suspension it was filtered to remove the solids. The filtrate was evaporated *in vacuo* to give the title compound (1.2 g). : ^1H NMR: ($CDCl_3$) δ 3.74 (m, 2H), 1.2-1.6 (m, 13H).

1g.) (1-Methyl-cyclopentyl)-acetaldehyde

To a solution of (1-methyl-cyclopentyl)-ethanol (Example 1f, 1.2 g, 9.37mmol) in CH_2Cl_2 (20 mL), Dess-Martin periodinane(1.2 g) was added. After stirring for 2 hours, solutions of sodium thiosulfate (10% in water, 0.50 mL) and saturated aqueous sodium bicarbonate (0.50 mL) were added simultaneously to the reaction. The mixture was then extracted with ethyl acetate (2 x). The organic layer was dried with $MgSO_4$, filtered, concentrated and purified via silica gel chromatography to give the title compound (1.1 g). ^1H NMR: ($CDCl_3$) δ 9.8 (s, 1H), 2.2 (s, 2H), 0.8-1.8 (m, 11H).

1h.) N-Boc-beta-(1-methylcyclopentyl)ala-OH

To a solution of (1-methyl-cyclopentyl)-acetaldehyde (Example 1g, 1.1 g, 8.73 mmol) in a mixture of ethanol (12 mL) and water (12 mL), potassium cyanide (624 mg, 9.6 mmol) and ammonium carbonate (2.26 g, 23.57 mmol) were added. The reaction mixture was stirred at 60 °C for 24 hours after which time the ethanol was removed in vacuo and the resultant aqueous solution was acidified to pH=1 with conc. HCl. The resultant white solid was collected by filtration, washed with water and dried under vacuum (420 mg). The product (420 mg) was refluxed in aqueous NaOH (aq.) (12 mL, 0.7 M) for 24 hours after which time the reaction mixture was concentrated to about 4 ml, and a solution of di-tert-butyldicarbonate 970 mg) in THF (10 mL) was added. After 2 hours, the THF was removed under vacuum, the residue was diluted with water (30 mL), and the mixture was washed with ether (2x). The aqueous phase was acidified to pH=1 with 1N aqueous HCl and then extracted with ethyl acetate (3x). The combined organic phase was washed with brine, dried, filtered, concentrated to give the title compound (300 mg). LC-MS m/z 271.2 (M^+).

1i.) (1S, 4R,7R)-4-Methyl-8-oxa-3-azabicyclo[5.1.0]octane-3-carboxylic acid benzyl ester

To a solution of (1R, 4R,7S)-4-methyl-8-oxa-3-azabicyclo[5.1.0]octane-3-carboxylic acid benzyl ester (25 g, 95.4 mmol) in a mixture of toluene (210 mL) and DMSO (210 mL), potassium acetate (93.5 g, 954 mmol), acetic acid (5.72 g, 95.4 mmol) and 18-crown-6 (12.6 g, 47.7 mmol) were added at room temperature. The reaction mixture was stirred at 110°C for 24 hours after which time the solvent was evaporated under reduced pressure. The residue was diluted with ethyl acetate and was washed with water, sodium bicarbonate (sat.) and brine. The combined organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure to give a mixture of products which was used directly in the next step without further purification (27.86 g). LC-MS m/z 322.0 (M^+).

To solution of the mixture compounds (from above) (27.86 g, 86.8 mmol) in methylene chloride (400 mL), methanesulfonyl chloride (10.12 ml, 130.2 mmol) and triethylamine (24.2 mL, 173.6 mmol)were added. The reaction mixture was stirred at room temperature for 5 hours. It was then partitioned between methylene chloride and water. The combined organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure to give a mixture of products which were used directly in the next step without further purification (30.5 g). LC-MS m/z 400.0 (M^+).

To a solution of the mixture of compounds (from above) (30.5 g, 76.2 mmol) in methanol (100 mL), 10 % potassium hydroxide solution (100mL) was added at room temperature. The reaction mixture was stirred at room temperature for 24 hours, after which time the solvent was removed under reduce pressure. The residue was partitioned between ethyl

acetate and water. The combined organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure to give a mixture of products. Silica gel chromatography of the mixture of epoxides (20%Ethyl acetate/80%Hexane) gave the title compound (7.47 g) and undesired epoxide product (10.5 g). LC-MS m/z 262 (M^+).

1j.) (2R, 5S, 6S)-5-Azido-6-hydroxy-2-methyl-azepane-1-carboxylic acid benzyl ester

A 1-liter round bottom flask was charged with (1S, 4R,7R)-4-methyl-8-oxa-3-azabicyclo[5.1.0]octane-3-carboxylic acid benzyl ester (Example 1i, 7.47 g, 28.3 mmol). Ethylene glycol (46 ml) was then added. Triethanolamine (23.7 ml, 169.8 mmol) was dissolved in H_2O (46 ml), then was added. NH_4Cl (4.54 g, 84.9 mmol), then sodium azide (5.52 g, 84.9 mmol) was added and the reaction was stirred behind a blast shield at 80° C overnight. The reaction mixture was cooled to RT, then poured into 10% aqueous NaCl. The mixture was extracted with CH_2Cl_2, and the combined organics were back extracted with aqueous $NaHCO_3$, then brine, dried with $MgSO_4$, filtered, concentrated *in vacuo*, and purified by flash column chromatography (20% to 33% ethyl acetate/hexanes, silica gel) to yield the title compound (7.4 g, 86%). LC-MS m/z 305.0 (M^+).

1k.) (2R, 5S, 6S)-5-Amino-6-hydroxy-2-methyl-azepane-1-carboxylic acid benzyl ester, HCl salt

(2R, 5S, 6S)-5-Azido-6-hydroxy-2-methyl-azepane-1-carboxylic acid benzyl ester (Example 1j, 6.6 g, 21.7 mmol) was dissolved in THF (100 ml) and H_2O (2.8 ml), then triphenylphosphine (8.5 g, 32.6 mmol) was added and the reaction was stirred at R.T overnight. The reaction mixture was concentrated *in vacuo*, and the remaining solid dissolved in MeOH (10 ml). 1 M HCl in Et_2O (20 ml) was added, then the solution was concentrated *in vacuo* to a solid. This was dissolved in a minimum amount of MeOH in a round bottle flask and the solution triturated with Et_2O (~500mL) to precipitate triphenylphospine oxide. The solid was removed via filtration and the above procedure repeated several times until no UV active component was being further extracted (<10% UV absorption of triphenylphospine oxide by LC-MS). The remaining solid was used in the next reaction without further purification (6.6 g, 91%). LC-MS m/z 279.2 (M^+).

1l.) (2R, 5S, 6S)-5-N-Bocamino-6-hydroxy-2-methyl-azepane-1-carboxylic acid benzyl ester

To a solution of (2R, 5S, 6S)-5-amino-6-hydroxy-2-methyl-azepane-1-carboxylic acid benzyl ester, HCl salt (Example 1k, 6.91 g, 22 mmol) in dioxane (74 mL), sodium hydroxide

(1.76 g, 44 mmol) and water (13 mL) were added. Then the reaction mixture was cooled to 0°C. Di-*tert*-butyl dicarbonate (5.28 g, 24.2 mmol) was added, and the reaction mixture was allowed to warm to room temperature for 16 hours. The solvent was evaporated, and the residue was diluted with ethyl acetate and washed with H_2O, 10% HCl solution, $NaHCO_3$(aq.) and brine. The combined organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure to give a crude product. Chromatography of the resulting solid on silica gel (30%Ethyl acetate/70%Hexane) gave the title compound (7.94 g, 95 %). LC-MS m/z 379.2 (M^+).

1m.) [(3S, 4S, 7R)-3-Hydroxy-7-methyl-azepan-4-yl]-carbamic acid tert-butyl ester

To a solution of (2R, 5S, 6S)-5-N-bocamino-6-hydroxy-2-methyl-azepane-1-carboxylic acid benzyl ester (Example 11, 7.94 g, 20.9 mmol) in ethanol (200 mL), palladium (10wt.% on activated carbon) (1.7 g) was added. The reaction mixture was hydrogenated at 45 psi for 5 hours. The reaction mixture was filtered through celite, concentrated in vacuo by rotary evaporation to give the title compound which was used without further purification (5.0 g, 97 %). LC-MS m/z 245.0 (M^+).

1n.) [(3S, 4S, 7R)-3-Hydroxy-7-methyl-1-(pyridine-2-sulfonyl)-azepan-4-yl]-carbamic acid tert-butyl ester

A solution of 2-mercaptopyridine (10 g, 90 mmol) in a mixture of conc. HCl (116 mL) and H_2O (34 mL) was cooled to 0°C. Chlorine gas was bubbled into the solution at 0°C for 3.0 hours. Ice was added to the reaction mixture, followed by extraction with cold ether (2x). The ether layer was washed with cold 10% $NaHCO_3$ solution, and cold brine. The ether layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure to give 2-pyridine sulfonyl chloride which was used without further purification (12.86 g, 80 %). LC-MS m/z 178.0 (M^+).

Triethyl amine (9.38 mL, 67.32 mmol) was added to a solution of [(3S, 4S, 7R)-3-hydroxy-7-methyl-azepan-4-yl]-carbamic acid *tert*-butyl ester (Example 1m, 5.0 g, 20.4 mmol) in methylene chloride (50 mL). The reaction mixture was cooled to 0°C, whereupon a solution of 2-pyridine sulfonyl chloride (3.26 g, 18.36 mmol) in methylene chloride (10 mL) was added dropwise. The resulting solution was stirred at room temperature for 4 hours. The reaction mixture was partitioned between methylene chloride and water. The aqueous phase extracted further with methylene chloride. The combined organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure to give a crude product. Chromatography of the resulting solid on silica gel (70%Ethyl acetate/30%Hexane) gave the desired product (5.6 g, 71 %). LC-MS m/z 386.0 (M^+).

1o.) (3S, 4S, 7R)-3-Hydroxy-7-methyl-1-(pyridine-2-sulfonyl)-azepan-3-ol, HCl salt

HCl in dioxane (4.0 M, 89 mL) was added to a stirred solution of [(3S, 4S, 7R)-3-hydroxy-7-methyl-1-(pyridine-2-sulfonyl)-azepan-4-yl]-carbamic acid *tert*-butyl ester (Example 1n, 5.6 g, 14.5 mL) in MeOH (30 mL). The reaction mixture was stirred for 2 hours at room temperature, then concentrated in vacuo to yield a white solid. This was used in the next reaction reaction without further purification (5.7 g). LC-MS m/z 286.0 (M^+).

1p.) 2-Amino-N-[(3S, 4S, 7R)-3-hydroxy-7-methyl-1-(pyridine-2-sulfonyl)-azepan-4 yl]-3-(1-methyl-cyclopentyl)-propionamide, HCl salt

To a solution of (3S,4S,7R)-4-amino-7-methyl-1-(pyridine-2-sulfonyl)-azepan-3-ol, HCl salt (Example 1o, 358 mg, 1.11 mmol) in DMF, N-Boc-beta-(1-methylcyclopentyl)ala-OH (Example 1h, 300 mg, 1.11 mmol), HBTU (547 mg, 1.47 mmol) and 4-methylmorpholine (561 mg, 5.55 mmol) were added. After the reaction mixture was stirred at room temperature for 16 hours, it was partitioned between ethyl acetate and water. The combined organic phase was washed with water, brine, dried ($MgSO_4$), filtered and concentrated. Column chromatography (5% methanol:CH_2Cl_2) of the residue provided the N-Boc title compound (220 mg, 37%). MS (m/z) 539.0 (M^+).

To a stirring solution of N-Boc-2-amino-N-[(3S, 4S, 7R)-3-hydroxy-7-methyl-1-(pyridine-2-sulfonyl)-azepan-4-yl]-3-(1-methyl-cyclopentyl)-propionamide (220 mg, 0.41 mmol) in methanol (1 mL) was added HCl (4M in dioxane) (2.54 mL). After stirring at room temperature for 2 hours, the mixture was concentrated, giving a white solid. The white solid was azeotroped with toluene (2x) and then concentrated to give the title compound as a solid (200 mg). MS (m/z) 439.0 (M^+).

1q.) Morpholine-4-carboxylic acid [1-[(3S, 4S, 7R)-3-hydroxy-7-methyl-1-(pyridine sulfonyl)-azepan-4-ylcarbamoyl]-2-(1-methyl-cyclopentyl)-ethyl]-amide

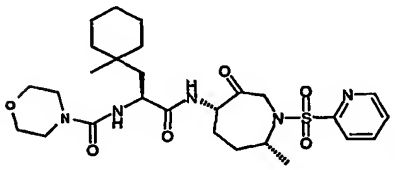
To a stirring solution of 2-amino-N-[(3S, 4S, 7R)-3-hydroxy-7-methyl-1-(pyridine-2-sulfonyl)-azepan-4-yl]-3-(1-methyl-cyclopentyl)-propionamide (Example 1p, 0.2 g, 0.46mmol) in CH_2Cl_2 (5 mL) were added 4-morpholinecarbonyl chloride (69 mg, 0.46 mmol) and triethyl amine (0.384 ml, 2.76 mmol). After stirring at room temperature for 16 hours, the reaction mixture was washed with water, brine, dried ($MgSO_4$), filtered and concentrated. Column chromatography (5% methanol:CH_2Cl_2) of the residue provided the title compound (120 mg, 47%). MS m/z 552.2 (M^+).

1r.) Morpholine 4-carboxylic acid {(S)-2-[1-methylcyclopentyl-1-(4S,7R)-7-methyl-3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide;

To a stirring solution of morpholine-4-carboxylic acid [1-[(3S, 4S, 7R)-3-hydroxy-7-methyl-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-2-(1-methyl-cyclopentyl)-ethyl]-amide (Example 1q, 100 mg, 0.18 mmol) in CH_2Cl_2 (2 mL) was added Dess-Martin periodinane (100 mg, 0.23 mmol). After stirring for 2 hours, solutions of sodium thiosulfate (10% in water, 0.50 mL) and saturated aqueous sodium bicarbonate (0.50 mL) were added simultaneously to the reaction. The mixture was then extracted with ethyl acetate (2 times). The organic layer was dried with $MgSO_4$, filtered, and concentrated. Column chromatography (5% methanol:CH_2Cl_2) of the residue provided the title compound (100 mg, 99%). This compound was purified on a preparative R,R-Whelk-O column by HPLC to yield the two diastereomers of the title compound as solids [first eluting (1A): 30 mg, second eluting (1B): 25 mg]. MS m/z 550.0 (M^+); The ^1H NMR data of 1A:^1H NMR (400Hz, $CDCl_3$): δ 8.78 (d, 1H), 8.0 (m, 2H), 7.53 (m, 1H), 6.9 (d, 1H), 5.1 (m, 1H), 4.91 (d, 1H), 4.80 (d, 1H), 4.40 (m, 2H), 3.9 (d, 1H), 3.70 (t, 4H), 3.40 (t, 4H), 2.2 (m, 3H), 0.93-1.93 (m, 17H). The ^1H NMR data of 1B:^1H NMR (400Hz, $CDCl_3$): δ 8.7 (d, 1H), 8.0 (m, 2H), 7.53 (m, 1H), 7.2 (d, 1H), 5.1 (m, 1H), 4.8 (d, 1H), 4.48 (d, 1H), 3.86 (d, 1H), 3.75 (m, 4H), 3.40 (m, 4H), 2.2 (m, 2H), 2.05 (m, 1H), 0.93-1.65 (m, 17H).

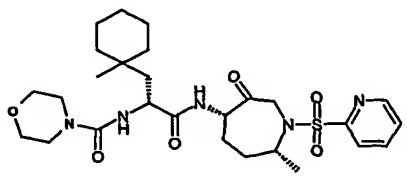
Example 2

Preparation of 2A: Morpholine 4-carboxylic acid {(S)-2-[1-methylcyclohexyl-1-(4S,7R)-7-methyl-3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide;



2A

Preparation of 2B: Morpholine 4-carboxylic acid {(L)-2-[1-methylcyclohexyl-1-(4S,7R)-7-methyl-3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide;



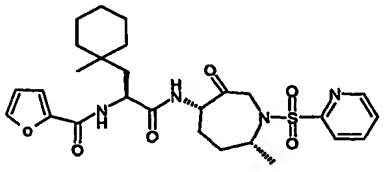
2B

Following the procedure of Example 1 (b-r), except substituting "1-methylcyclohexyl" for "1-methylcyclopentyl" gave the title compound: ^{1}HNMR data of 2A: ^1H NMR (400Hz,

$CDCl_3$): δ 8.72 (d, 1H), 7.95 (m, 2H), 7.5 (d, 1H), 6.91 (d, 1H), 5.10 (m, 1H), 4.95 (d, 1h), 4.75 (d, 1H), 4.40 (m, 2H), 3.82 (d, 1H), 3.70 (t, 4h), 3.40 (t, 4H), 2.20 (m, 3H), 0.95-1.80 (m, 19H). The ^1H NMR data of 2B: ^1H NMR (400Hz, $CDCl_3$): δ 8.70 (d, 1H), 7.95 (m, 2H), 7.52 (m, 1H), 7.2 (d, 1H), 5.10 (m, 1H), 4.83 (d, 1H), 4.70 (d, 1H), 4.44 (m, 2H), 3.82 (d, 1H), 3.70 (t, 4H), 3.40 (t, 4H), 2.2 (m, 2H), 1.9 (m, 1H), 0.95-1.5 (m, 8H).

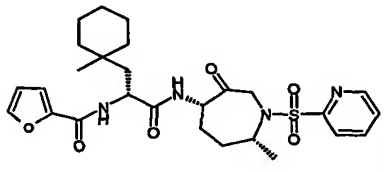
Example 3

Preparation of 3A: Furan-carboxylic acid {(S)-2-[1-methylcyclohexyl-1-(4S,7R)-7-methyl-3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide;



3A

Preparation 3B: Furan-carboxylic acid {(L)-2-[1-methylcyclohexyl-1-(4S,7R)-7-methyl-3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide;



3B

3a) Furan-2-carboxylic acid [1-[(3S, 4S, 7R)-3-hydroxy-7-methyl-1-(pyridine-2 sulfonyl)-azepan-4-ylcarbamoyl]-2-(1-methyl-cyclopentyl)-ethyl]-amide

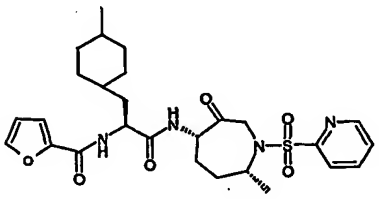
To a solution of 2-amino-N-[(3S, 4S, 7R)-3-hydroxy-7-methyl-1-(pyridine-2-sulfonyl)-azepan-4-yl]-3-(1-methyl-cyclohexyl)-propionamide, HCl salt (Example 2o, 357 mg, 0.73 mmol) in DMF, 2-furoic acid (81.8 mg, 0.73 mmol), HBTU (360 mg, 0.95 mmol) and 4-methylmorpholine (369 mg, 3.65 mmol) were added. After the reaction mixture was stirred at room temperature for 16 hours, it was partitioned between ethyl acetate and water. The combined organic phase was washed with water, brine, dried ($MgSO_4$), filtered and concentrated. Column chromatography (5% methanol:CH_2Cl_2) of the residue provided the N-Boc title compound (376 mg, 94%)MS m/z 547.2 (M^+).

3b) Following the procedure of Example 1 (b-p, r), except substituting "4-methylcyclohexyl" for "1-methylcyclopentyl" and "furan-2-carboxylic acid" for "morpholine 4-carboxylic acid" gave the title compound: The ^1H NMR data of 3A: ^1H NMR (400Hz, $CDCl_3$): δ 8.72 (d, 1H), 8.0 (m, 2H), 7.54 (t, 1H), 7.50 (s, 1H), 7.15 (s, 1H), 6.96 (d, 1H), 6.70 (d, 1H), 6.52 (d, 1H), 5.1 (m, 1H), 4.75 (d, 1H), 4.66 (m, 1H), 4.45 (m, 1H), 3.85 (d, 1H), 2.2 (m, 3H),

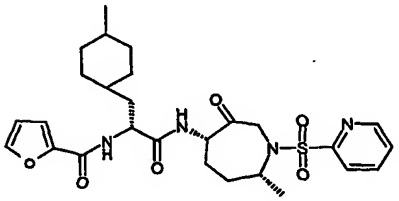
1.95 (m, 1H), 0.95-1.60 (m, 18H). The ^{1}H NMR data of 3B:^{1}H NMR (400Hz, $CDCl_3$): δδ 8.72 (d, 1H), 8.0 (m, 2H), 7.5 (m, 2H), 7.12 (m, 2H), 6.6 (d, 1H), 6.54 (d, 1H), 5.10 (m, 1H), 4.66 (m, 2H), 4.42 (m, 1H), 3.80 (d, 1H), 2.2 (m, 3H), 2.08 (m, 1H), 0.95-1.60 (m, 18H).

Example 4

Preparation 4A: Furan-carboxylic acid {(S)-2-[4-methylcyclohexyl-1-(4S,7R)-7-methyl-3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide;



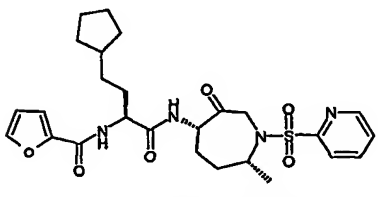
Preparation 4B: Furan-carboxylic acid {(L)-2-[4-methylcyclohexyl-1-(4S,7R)-7-methyl-3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide;



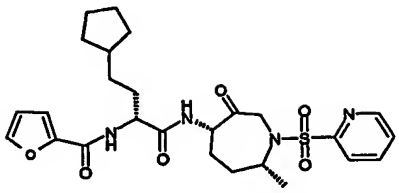
Following the procedure of Example 3 (f-r), except substituting "4-methylcyclohexyl" for "1-methylcyclohexyl" gave the title compound: The ^{1}H NMR data of 4A:^{1}H NMR (400Hz, $CDCl_3$): δ 8.75 (d, 1H), 8.0 (m, 2H), 7.60 (m, 2H), 7.1 (d, 1H), 6.90 (d, 1H), 6.75 (d, 1H), 6.5 (s, 1H), 5.15 (m, 1H), 4.80 (d, 1H), 4.70 (m, 1H), 4.45 (m, 1H), 3.9 (d, 1H), 2.2 (m, 3H), 0.85-1.90 (m, 19H). The ^{1}H NMR data of 4B:^{1}H NMR (400Hz, $CDCl_3$): δ 8.75 (d, 1H), 8.0 (m, 2H), 7.50 (m, 2H), 7.20 (d, 1H), 7.06 (d, 1H), 6.70 (m, 1H), 6.5 (s, 1H), 5.1 (m, 1H), 4.70 (m, 2H), 4.45 (m, 1H), 3.85 (d, 1H), 2.2 (m, 3H), 0.85-1.90 (m, 19H).

Example 5

Preparation of 5A: Furan-carboxylic acid {(S)-2-[homocyclopentyl-1-(4S,7R)-7-methyl-3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide;



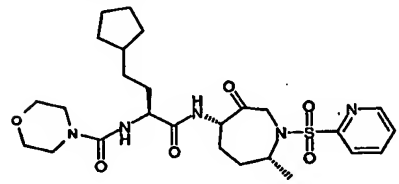
Preparation of 5B: furan-carboxylic acid {(L)-2-[homocyclopentyl-1-(4S,7R)-7-methyl-3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide;



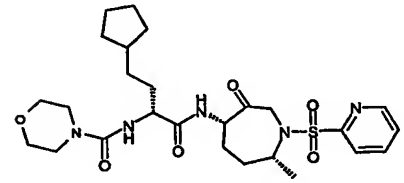
Following the procedure of Example 3 (f-r), except substituting "homocyclopentyl" for "1-methylcyclohexyl" gave the title compound: The ^{1}H NMR data of 5A:^{1}H NMR (400Hz, $CDCl_3$): δ 8.75 (d, 1H), 8.0 (d, 1H), 7.95 (t, 1H), 7.55 (m, 1H), 7.48 (s, 1H), 7.15 (d, 1H), 6.85 (t, 2H), 6.54 (d, 1H), 5.15 (d, 1H), 4.80 (d, 1H), 4.60 (m, 1H), 4.45 (m, 1H), 3.85 (d, 1H), 2.20 (m, 2H), 1.90 (m, 1H), 1.0-1.83 (m, 17H). The ^{1}H NMR data of 5B:^{1}H NMR (400Hz, $CDCl_3$): δ 8.70 (d, 1H), 8.0 (d, 1H), 7.95 (t, 1H), 7.5 (m, 2H), 7.2 (d, 1H), 7.0 (d, 1H), 6.8 (d, 1H), 6.5 (d, 1H), 5.15 (m, 1H), 4.75 (d, 1H), 4.6 (q, 1H), 4.45 (q, 1H), 3.85 (d, 1H), 2.2 (m, 2H), 2.0 (m, 1H), 1.0-1.80 (m, 17H).

Example 6

Preparation of 6A: Morpholine 4-carboxylic acid {(S)-2-[homocyclopentyl-1-(4S,7R)-7-methyl-3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide;



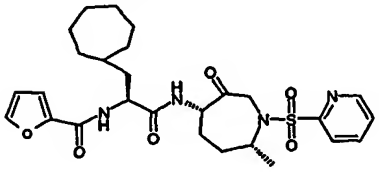
Preparation of 6B: morpholine 4-carboxylic acid {(L)-2-[homocyclopentyl-1-(4S,7R)-7-methyl-3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide;



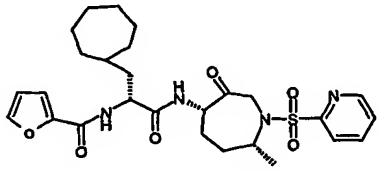
Following the procedure of Example 1 (f-r), except substituting "homocyclopentyl" for "1-methylcyclopentyl" gave the title compound: The ^{1}H NMR data of 6A:^{1}H NMR (400Hz, $CDCl_3$): δ 8.7 (d, 1H), 7.9 (m, 2H), 7.50 (m, 1H), 7.0 (m, 1H), 5.30 (d, 1H), 5.10 (m, 1H), 4.70 (d, 1H), 4.35 (m, 2H), 3.80 (d, 1H), 3.65 (t, 4H), 3.35 (t, 4H), 2.20 (m, 3H), 0.90-1.75 (m, 17H). The ^{1}H NMR data of 6B:^{1}H NMR (400Hz, $CDCl_3$): δ 8.70 (d, 1H), 8.0 (d, 1H), 7.95 (t, 1H), 7.50 (m, 1H), 7.0 (d, 1H), 5.10 (m, 1H), 5.0 (d, 1H), 4.70 (d, 1H), 4.50 (m, 1H), 4.40 (m, 1H), 3.85 (d, 1H), 3.70 (t, 4H), 3.40 (t, 4H), 2.20 (m, 3H), 1.0-1.9 (m, 17H).

Example 7

Preparation of 7A: furan-carboxylic acid {(S)-2-[cycloheptyl-1-(4S,7R)-7-methyl-3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide;



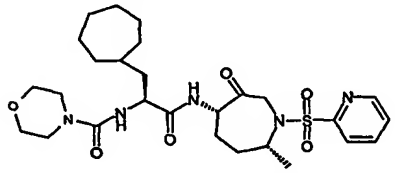
Preparation of 7B: furan-carboxylic acid {(L)-2-[cycloheptyl-1-(4S,7R)-7-methyl-3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide;



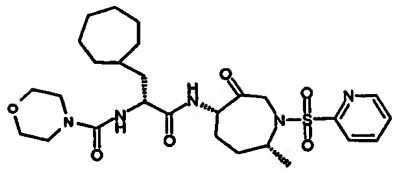
Following the procedure of Example 3 (f-r), except substituting "cycloheptyl" for "1-methylcyclohexyl" gave the title compound: The ^{1}H NMR data of 7A: ^{1}H NMR (400Hz, $CDCl_3$): δ 8.70 (d, 1H), 8.0 (d, 1H), 7.90 (t, 1H), 7.55 (m, 1H), 7.5 (s, 1H), 7.15 (d, 1H), 6.90 (d, 1H), 6.80 (d, 1H), 6.5 (d, 1H), 5.15 (m, 1H), 4.80 (d, 1H), 4.60 (q, 1H), 4.40 (q, 1H), 3.9 (d, 1H), 2.2 (m, 2H), 1.0-1.80 (m, 20H).The ^{1}H NMR data of 7B: ^{1}H NMR (400Hz, $CDCl_3$): δ 8.70 (d, 1H), 8.0 (d, 1H), 7.90 (t, 1H), 7.55 (d, 1H), 7.50 (s, 1H), 7.15 (d, 1H), 7.05 (d, 1H), 6.7 (d, 1H), 6.5 (d, 1H), 5.10 (m, 1H), 4.75 (d, 1H), 4.65 (m, 1H), 4.5 (m, 1H), 3.85 (d, 1H), 2.20 (m, 2H), 1.0-1.90 (m, 20H).

Example 8

Preparation of 8A: morpholine 4-carboxylic acid {(S)-2-[cycloheptyl-1-(4S,7R)-7-methyl-3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide;



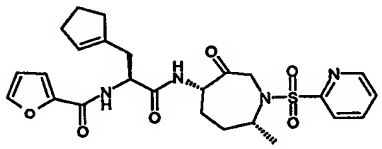
Preparation of 8B: morpholine 4-carboxylic acid {(L)-2-[cycloheptyl-1-(4S,7R)-7-methyl-3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide;



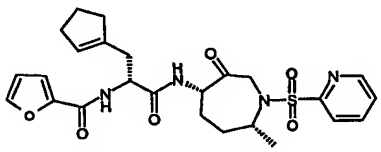
Following the procedure of Example 1 (f-r), except substituting "cycloheptyl" for "1-methylcyclopentyl" gave the title compound: The ^{1}H NMR data of 8A: ^{1}H NMR (400Hz, $CDCl_3$): δ 8.75 (d, 1H), 8.0 (m, 2H), 7.55 (m, 1H), 6.85 (m, 1H), 5.15 (m, 1H), 4.95 (m, 1H), 4.80 (d, 1H), 4.45 (m, 2H), 3.90 (d, 1H), 3.7 (t, 4H), 3.40 (t, 4H), 2.2 (m, 3H), 1.0-1.80 (m, 19H). The ^{1}H NMR data of 8B: ^{1}H NMR (400Hz, $CDCl_3$): δ 8.75 (d, 1H), 8.0 (m, 2H), 7.55 (m, 1H), 7.10 (m, 1H), 5.10 (m, 1H), 4.80 (m, 1H), 4.75 (d, 1H), 4.40 (m, 2H), 3.85 (d, 1H), 3.70 (t, 4H), 3.40 (t, 4H), 2.2 (m, 3H), 1.0-1.80 (m, 19H).

Example 9

Preparation of 9A: furan-carboxylic acid {(S)-2-[cyclopentenyl-1-(4S,7R)-7-methyl-3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide;



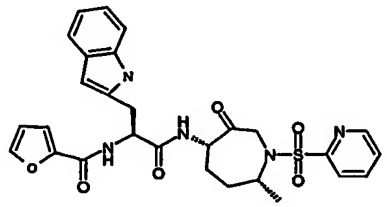
Preparation of 9B: furan-carboxylic acid {(L)-2-[cyclopentenyl-1-(4S,7R)-7-methyl-3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide;



Following the procedure of Example 3 (f-r), except substituting "cyclopentenyl" for "1-methylcyclohexyl" gave the title compound: The ^{1}H NMR data of 9A: ^{1}H NMR (400Hz, $CDCl_3$): δ 8.7 (d, 1H), 8.0 (m, 2H), 7.5 (m, 2H), 7.1 (d, 1H), 7.0 (d, 1H), 6.85 (d, 1H), 6.5 (d, 1H), 5.6 (m, 1H), 5.1 (m, 1H), 4.7 (m, 2H), 4.4 (m, 1H), 3.80 (m, 1H), 2.7 (m, 2H), 2.3 (m, 4H), 2.2 (m, 2H), 1.9 (m, 2H), 1.0-1.7 (m, 5H). The ^{1}H NMR data of 9B: ^{1}H NMR (400Hz, $CDCl_3$): δ 8.7 (d, 1H), 8.0 (m, 2H), 7.5 (m, 2H), 7.2 (d, 1H), 7.1 (d, 1H), 6.80 (d, 1H), 6.5 (d, 1H), 5.5 (d, 1H), 5.1 (m, 1H), 4.7 (m, 2H), 4.4 (m, 1H), 3.8 (d, 1H), 2.7 (m, 2H), 2.3 (m, 4H), 2.2 (m, 2H), 1.9 (m, 2H), 1.0-1.6 (m, 5H).

Example 10

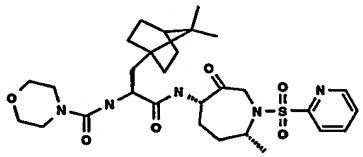
Preparation of 10A: furan-carboxylic acid {(S)-2-[tryptophanyl-1-(4S,7R)-7-methyl-3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide;



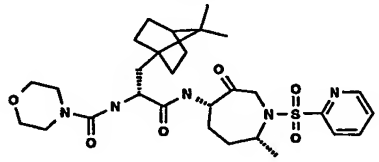
Following the procedure of Example 3 (f-r), except substituting "tryptophanyl" for "1-methylcyclhexyl" gave the title compound: ^{1}H NMR (400Hz, $CDCl_3$): δ 8.65 (m, 2H), 8.05 (d, 1H), 7.9 (t, 1H), 7.8 (d, 1H), 7.5 (m, 1H), 7.45 (s, 1H), 7.40 (d, 1H), 7.35 (d, 1H), 7.2 (m, 4H), 6.5 (d, 1H), 5.7 (d, 1H), 5.0 (m, 1H), 3.85 (m, 2H), 3.65 (m, 1H), 3.45 (m, 1H), 3.2 (m, 1H), 3.05 (m, 1H), 2.40 (d, 1H), 0.8-1.6 (m, 6H).

Example 11

Preparation of 11A: morpholine 4-carboxylic acid {(S)-2-(7,7-dimethyl-bicyclo[2.2.1]hepty-1-yl)-1-[(4S,7R)-7-methyl-3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide;



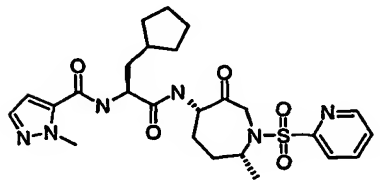
Preparation of 11B: morpholine 4-carboxylic acid {(L)-2-(7,7-dimethyl-bicyclo[2.2.1]hepty-1-yl)-1-[(4S,7R)-7-methyl-3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide;



Following the procedure of Example 1 (f-r), except substituting "2-(7,7-dimethyl-bicyclo[2.2.1]hepty-1-yl)" for "1-methylcyclopentyl" gave the title compound: The ^{1}H NMR data of 11A: ^{1}H NMR (400Hz, $CDCl_3$): δ 8.65 (d, 1H), 7.9 (m, 2H), 7.40 (m, 1H), 6.9 (d, 1H), 4.9 (m, 2H), 4.65 (d, 1H), 4.3 (m, 2H), 3.75 (d, 1H), 3.6 (t, 4H), 3.3 (t, 4H), 2.1 (m, 2H), 0.8-1.7 (m, 22H). : The ^{1}H NMR data of 11B: ^{1}H NMR (400Hz, $CDCl_3$): δ 8.70 (d, 1H), 8.0 (m, 2H), 7.55 (d, 1H), 7.2 (d, 1H), 5.1 (m, 1H), 4.7 (m, 2H), 4.4 (m, 2H), 3.85 (d, 1H), 3.7 (t, 4H), 3.4 (t, 4H), 2.2 (m, 2H), 0.9-1.9 (m, 22H).

Example 12

Preparation of 12c: 2-methyl-2H-pyrazole-3-carboxylic acid {(S)-2-cyclopentyl-1-[(4S, 7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide



12a.) (S)-2-*tert*-Butoxycarbonylamino-3-cyclopentyl-propionic acid

The solution of (S)-2-amino-3-cyclopentyl-propionic acid (3.0g, 19.1 mmol) in 30 mL of 1,4-dioxane and water (1:1 ratio) was cooled to 0°C, sodium hydroxide (1.5g, 38 mmol) and di-tert-butyldicarbonate (5.0g, 22.9 mmol) were added. After stirring at room temperature overnight, the mixture was adjusted to pH 1 with concentrated HCl. The resulting mixture was extracted with ethyl acetate (3x), the combined organic phase was washed with brine, dried over $MgSO_4$, filtered, and concentrated to give the title compound (4.9 g). LC-MS m/z 258.2 (M^+), 1.84 min.

12b.) (S)-2-amino-3-cyclopentyl-N-[(3S, 4S, 7R)-3-hydroxy-7-methyl-1-(pyridine-2-sulfonyl)-azepan-4-yl]-propionamide HCl salt

Following the procedure of Example 1p, (S)-2-*tert*-butoxycarbonylamino-3-cyclopentyl-propionic acid (4.42g, 17.2mmol) and (3S,4S,7R)-4-amino-7-methyl-1-(pyridine-2-sulfonyl)-azepan-3-ol, HCl salt (Example 1o, 7.26g, 22.5 mmol) were reacted, followed by deprotection with 4N HCl in 1,4-dioxane to give title product (7.9g, 72%). LC-MS m/z 452.0 (M^+), 1.54 min.

12c.) 2-Methyl-2H-pyrazole-3-carboxylic acid {(S)-2-cyclopentyl-1-[(4S, 7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide

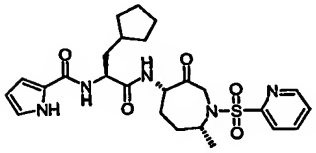
To a solution of (S)-2-amino-3-cyclopentyl-N-[(3S, 4S, 7R)-3-hydroxy-7-methyl-1-(pyridine-2-sulfonyl)-azepan-4-yl]-propionamide HCl salt (Example 12b, 125 mg, 0.27 mmol) in DMF, 2-methyl-2H-pyrazole-3-carboxylic acid (33 mg, 0.26 mmol), HBTU (128mg, 0.34 mmol) and 4-methylmorpholine (143 µl, 1.3 mmol) were added. After the reaction mixture was stirred at room temperature for 16 hours, it was partitioned between ethyl acetate and water. The combined organic phase was washed with water, brine, dried over $MgSO_4$, filtered and

concentrated. Column chromatography (5% methanol:CH_2Cl_2) of the residue provided 2-methyl-2H-pyrazole-3-carboxylic acid {(S)-2-cyclopentyl-1-[(3S, 4S, 7R)-7-methyl-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide (74 mg, 51%). MS (m/z) 533.0 (M^+), 1.88 min.

To a stirring solution 2-methyl-2H-pyrazole-3-carboxylic acid {(S)-2-cyclopentyl-1-[(3S, 4S, 7R)-7-methyl-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide (74 mg, 0.14 mmol) in CH_2Cl_2 (2 mL) was added Dess-Martin periodinane (77 mg, 0.18 mmol). After stirring for 3 hours, the mixture was concentrated. The residue was diluted with ethyl acetate and washed with water (2x). The organic layer was dried with $MgSO_4$, filtered, and concentrated. Column chromatography (5% methanol:CH_2Cl_2) of the residue, followed by recrystallization from dichloromethane and hexane provided the title compound (50 mg, 67%). LC-MS m/z 530.6 (M^+), 1.85 min.

Example 13

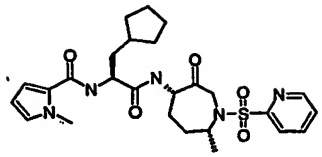
Preparation of 13: 1H-pyrazole-2-carboxylic acid {(S)-2-cyclopentyl-1-[(4S, 7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide



Following the general procedure described in Example 12c, (S)-2-amino-3-cyclopentyl-N-[(3S, 4S, 7R)-3-hydroxy-7-methyl-1-(pyridine-2-sulfonyl)-azepan-4-yl]-propionamide HCl salt (Example 12b, 200 mg, 0.43 mmol) was coupled with 1H-pyrrole-2-carboxylic acid (53mg, 0.49mmol), followed by oxidation with Dess-Martin periodinane (135mg, 0.32mmol) to give the title compound (50mg, 23%). LC-MS m/z 516.2 (M^+), 1.94 min.

Example 14

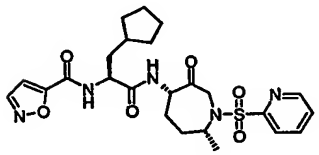
Preparation of 14: 1-Methyl-1H-pyrrole-2-carboxylic acid {(S)-2-cyclopentyl-1-[(4S, 7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide



Following the general procedure described in Example 12c, (S)-2-amino-3-cyclopentyl-N-[(3S, 4S, 7R)-3-hydroxy-7-methyl-1-(pyridine-2-sulfonyl)-azepan-4-yl]-propionamide HCl salt (Example 12b, 150 mg, 0.33 mmol) was coupled with 1-methyl-1H-pyrrole-2-carboxylic acid (50mg, 0.40mmol), followed by oxidation with Dess-Martin periodinane (182mg, 0.43mmol) to give the title compound (20mg, 18%). LC-MS m/z 530.0(M^+), 2.08 min.

Example 15

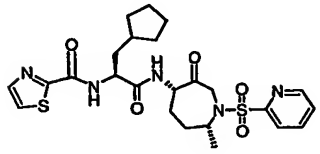
Preparation of 15: Isoxazole-5-carboxylic acid {(S)-2-cyclopentyl-1-[(4S, 7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide



Following the general procedure described in Example 12c, (S)-2-amino-3-cyclopentyl-N-[(3S, 4S, 7R)-3-hydroxy-7-methyl-1-(pyridine-2-sulfonyl)-azepan-4-yl]-propionamide HCl salt (Example 12b, 100 mg, 0.22 mmol) was coupled with isoxazole-5-carboxylic acid (25mg, 0.22mmol), followed by oxidation with Dess-Martin periodinane (115mg, 0.27mmol) to give the title compound (20mg, 18%). LC-MS m/z 518 (M^+), 1.88 min.

Example 16

Preparation of 16b: Thiazole-2-carboxylic acid {(S)-2-cyclopentyl-1-[(4S, 7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide



16a.) Thiazole-2-carboxylic acid

The mixture of thiazole-2-carboxylic acid ethyl ester (100mg, 0.64mmol) and lithium hydroxide monohydrate (134mg, 3.18mmol) in 5mL of methanol was stirred at room

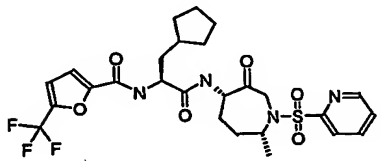
temperature for 16 hours. After removing solvent, the residue was acidified with aq. 1N HCl, extracted with ethyl acetate (2x), washed with brine. The combined organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure to give crude material which was used directly in the next step without further purification (53mg).

16b.) Thiazole-2-carboxylic acid {(S)-2-cyclopentyl-1-[(4S, 7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide

Following the general procedure described in Example 12c, (S)-2-amino-3-cyclopentyl-N-[(3S, 4S, 7R)-3-hydroxy-7-methyl-1-(pyridine-2-sulfonyl)-azepan-4-yl]-propionamide HCl salt (Example 12b, 94 mg, 0.20 mmol) was coupled with thiazole-2-carboxylic acid (26mg, 0.20mmol), followed by oxidation with Dess-Martin reagent (121mg, 0.29mmol) to give the title compound (30mg, 28%). LC-MS m/z 534.2(M^+), 2.04 min.

Example 17

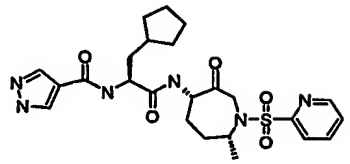
Preparation of 17: 5-trifluoromethyl-furan-2-carboxylic acid {(S)-2-cyclopentyl-1-[(4S, 7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide



Following the general procedure described in Example 12c, (S)-2-amino-3-cyclopentyl-N-[(3S, 4S, 7R)-3-hydroxy-7-methyl-1-(pyridine-2-sulfonyl)-azepan-4-yl]-propionamide HCl salt (Example 12b, 150 mg, 0.33 mmol) was coupled with 5-trifluoromethyl-furan-2-carboxylic acid (72mg, 0.40mmol), followed by oxidation with Dess-Martin periodinane (182mg, 0.43mmol) to give the title compound (29mg, 15%). LC-MS m/z 585.0(M^+), 2.25 min.

Example 18

Preparation of 18b: 1H-pyrazole-4-carboxylic acid {(S)-2-cyclopentyl-1-[(4S, 7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide



18a.) Pyrazole-1,4-dicarboxylic acid-1-tert-butyl ester

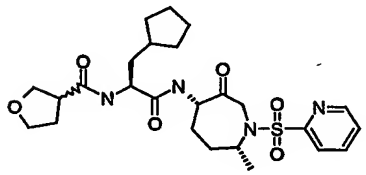
Following the general procedure in Example 12a, 1H-pyrazole-4-carboxylic acid (300mg, 2.68mmol), sodium hydroxide (214mg, 5.36mmol) and di-tert-butyldicarbonate (700mg, 2.68mmol) were reacted to give the title compound (153mg, 27%). ^{1}H NMR (400Hz, CDCl3) δ 8.66(s, 1H), 8.14 (s, 1H), 1.70 (s, 9H).

18b.) 1H-Pyrazole-4-carboxylic acid {(S)-2-cyclopentyl-1-[(4S, 7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide

Following the general procedure described in Example 12c, (S)-2-amino-3-cyclopentyl-N-[(3S, 4S, 7R)-3-hydroxy-7-methyl-1-(pyridine-2-sulfonyl)-azepan-4-yl]-propionamide HCl salt (Example 12b, 166 mg, 0.36 mmol) was coupled with pyrazole-1,4-dicarboxylic acid-1-tert-butyl ester (77mg, 0.36mmol), followed by oxidation with Dess-Martin periodinane (182mg, 0.43mmol) and then removing the tert-butoxycarbonyl protecting group with 4N HCl to give the title compound (49mg, 26%). LC-MS m/z 517.2 (M^+), 1.70 min.

Example 19

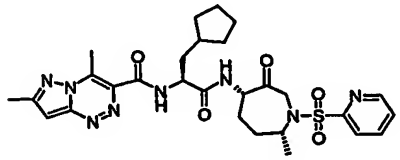
Preparation of 19: tetrahydrofuran-3-carboxylic acid {(S)-2-cyclopentyl-1-[(4S, 7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide



Following the general procedure described in Example 12c, (S)-2-amino-3-cyclopentyl-N-[(3S, 4S, 7R)-3-hydroxy-7-methyl-1-(pyridine-2-sulfonyl)-azepan-4-yl]-propionamide HCl salt (Example 12b, 200mg, 0.43 mmol) was coupled with tetrahydro-furan-3-carboxylic acid (75mg, 0.65mmol), followed by oxidation with Dess-Martin periodinane (244mg, 0.57mmol) to give the title compound (88mg, 39%). LC-MS m/z 521.2(M^+), 1.79 min.

Example 20

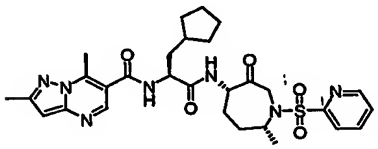
Preparation 20: 4,7-dimethyl-pyrazolo[5,1-c][1,2,4]triazine-3-carboxylic acid {(S)-2-cyclopentyl-1-[(4S,7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide



Following the general procedure described in Example 12c, (S)-2-amino-3-cyclopentyl-N-[(3S, 4S, 7R)-3-hydroxy-7-methyl-1-(pyridine-2-sulfonyl)-azepan-4-yl]-propionamide HCl salt (Example 12b, 150mg, 0.33mmol) was coupled with 4,7-dimethyl-pyrazolo[5,1-c][1,2,4]triazine-3-carboxylic acid (77mg, 0.40mmol), followed by oxidation with Dess-Martin periodinane (182mg, 0.43mmol) to give the title compound (3mg, 2%). LC-MS m/z 597.0 (M^+), 2.13 min.

Example 21

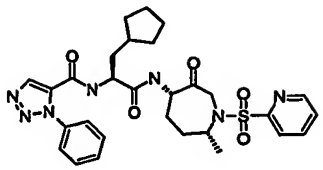
Preparation of 21: 2,7-dimethyl-pyrazolo[5,1-a]pyrimidine-6-carboxylic acid {(S)-2-cyclopentyl-1-[(4S,7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide



Following the general procedure described in Example 12c, (S)-2-amino-3-cyclopentyl-N-[(3S, 4S, 7R)-3-hydroxy-7-methyl-1-(pyridine-2-sulfonyl)-azepan-4-yl]-propionamide HCl salt (Example 12b, 150mg, 0.33mmol) was coupled with 2,7-dimethyl-pyrazolo[5,1-a]pyrimidine-6-carboxylic acid (70mg, 0.36mmol), followed by oxidation with Dess-Martin periodinane (210mg, 0.49mmol) to give the title compound (80mg, 41%). LC-MS m/z 596.0 (M^+), 1.92 min.

Example 22

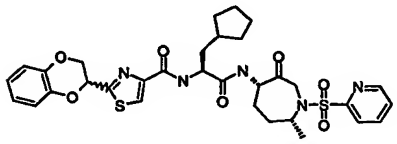
Preparation of 22: 3-Phenyl-3H-[1,2,3]triazole-4-carboxylic acid {(S)-2-cyclopentyl-1-[(4S, 7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide



Following the general procedure described in Example 12c, (S)-2-amino-3-cyclopentyl-N-[(3S, 4S, 7R)-3-hydroxy-7-methyl-1-(pyridine-2-sulfonyl)-azepan-4-yl]-propionamide HCl salt (Example 12b, 180mg, 0.39mmol) was coupled with 3-phenyl-3H-[1,2,3]triazole-4-carboxylic acid (81mg, 0.43mmol), followed by oxidation with Dess-Martin periodinane (225mg, 0.53mmol) to give the title compound (77mg, 37%). LC-MS m/z 594.2 (M^+), 2.02 min.

Example 23

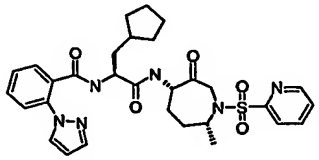
Preparation of 23: 2-(2,3-Dihydro-benzo[1,4]dioxin-2-yl)-thiazole-4-carboxylic acid {(S)-2-cyclopentyl-1-[(4S,7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide



Following the general procedure described in Example 12c, (S)-2-amino-3-cyclopentyl-N-[(3S, 4S, 7R)-3-hydroxy-7-methyl-1-(pyridine-2-sulfonyl)-azepan-4-yl]-propionamide HCl salt (Example 12b, 150mg, 0.33mmol) was coupled with 2-(2,3-dihydro-benzo[1,4]dioxin-2-yl)-thiazole-4-carboxylic acid (99mg, 0.37mmol), followed by oxidation with Dess-Martin periodinane (230mg, 0.54mmol) to give the title compound (96mg, 41%). LC-MS m/z 668.0 (M^+), 2.42min.

Example 24

Preparation of 24: N-{(S)-2-cyclopentyl-1-[(4S,7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-2-pyrazol-1-yl-benzamide

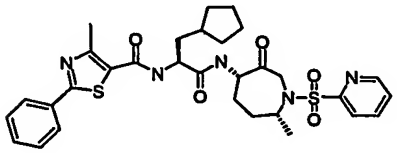


Following the general procedure described in Example 12c, (S)-2-amino-3-cyclopentyl-N-[(3S, 4S, 7R)-3-hydroxy-7-methyl-1-(pyridine-2-sulfonyl)-azepan-4-yl]-propionamide HCl salt (Example 12b, 150mg, 0.33mmol) was coupled with 2-pyrazol-1-yl-

benzoic acid (75mg, 0.40mmol), followed by oxidation with Dess-Martin periodinane (182mg, 0.43mmol) to give the title compound (30mg, 15%). LC-MS m/z 593.0 (M^+), 2.00 min.

Example 25

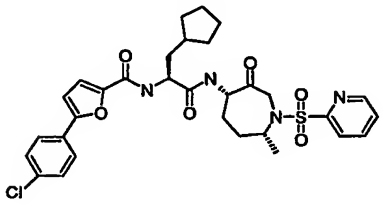
Preparation of 25: 4-Methyl-2-phenyl-thiazole-5-carboxylic acid {(S)-2-cyclopentyl-1-[(4S, 7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide



Following the general procedure described in Example 12c, (S)-2-amino-3-cyclopentyl-N-[(3S, 4S, 7R)-3-hydroxy-7-methyl-1-(pyridine-2-sulfonyl)-azepan-4-yl]-propionamide HCl salt (Example 12b, 150mg, 0.33mmol) was coupled 4-methyl-2-phenyl-thiazole-5-carboxylic acid (88mg, 0.40mmol), followed by oxidation with Dess-Martin periodinane (182mg, 0.43mmol) to give the title compound (117mg, 57%). LC-MS m/z 624.2 (M^+), 2.50 min.

Example 26

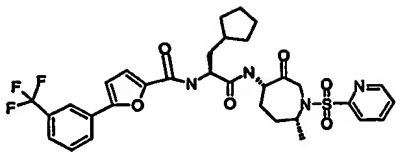
Preparation of 26: 5-(4-Chloro-phenyl)-furan-2-carboxylic acid {(S)-2-cyclopentyl-1-[(4S, 7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide



Following the general procedure described in Example 12c, (S)-2-amino-3-cyclopentyl-N-[(3S, 4S, 7R)-3-hydroxy-7-methyl-1-(pyridine-2-sulfonyl)-azepan-4-yl]-propionamide HCl salt (Example 12b, 150mg, 0.33mmol) was coupled 5-(4-chloro-phenyl)-furan-2-carboxylic acid (82mg, 0.37mmol), followed by oxidation with Dess-Martin periodinane (210mg, 0.50mmol) to give the title compound (82mg, 40%). LC-MS m/z 627.2 (M^+), 2.57 min.

Example 27

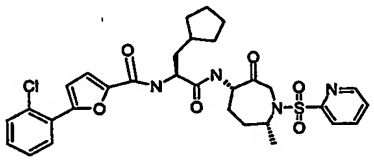
Preparation of 27: 5-(3-trifluoromethyl-phenyl)-furan-2-carboxylic acid {(S)-2-cyclopentyl-1-[(4S, 7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide



Following the general procedure described in Example 12c, (S)-2-amino-3-cyclopentyl-N-[(3S, 4S, 7R)-3-hydroxy-7-methyl-1-(pyridine-2-sulfonyl)-azepan-4-yl]-propionamide HCl salt (Example 12b, 100mg, 0.22mmol) was coupled 5-(3-trifluoromethyl-phenyl)-furan-2-carboxylic acid (56mg, 0.22mmol), followed by oxidation with Dess-Martin periodinane (121mg, 0.29mmol) to give the title compound (60mg, 40%). LC-MS m/z 661.2 (M^+), 2.57 min.

Example 28

Preparation of 28b: 5-(2-Chloro-phenyl)-furan-2-carboxylic acid {(S)-2-cyclopentyl-1-[(4S, 7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide



28a.) 5-Bromo-furan-2-carboxylic acid {(S)-2-cyclopentyl-1-[(4S, 7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide

Following the general procedure described in Example 12c, (S)-2-amino-3-cyclopentyl-N-[(3S, 4S, 7R)-3-hydroxy-7-methyl-1-(pyridine-2-sulfonyl)-azepan-4-yl]-propionamide HCl salt (Example 12b, 1.0g, 2.17mmol) was coupled 5-bromo-furan-2-carboxylic acid (415mg, 2.17mmol) to give the title compound (780mg, 60%). LC-MS m/z 597.0(M^+), 1.99 min.

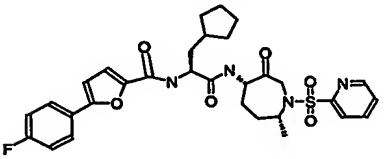
28b.) 5-(2-Chloro-phenyl)-furan-2-carboxylic acid {(S)-2-cyclopentyl-1-[(4S, 7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide

The mixture of 5-bromo-furan-2-carboxylic acid {(S)-2-cyclopentyl-1-[(4S, 7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide (25mg, 0.04mmol), 2-chlorophenylboronic acid (7mg, 0.04mmol), tetrakis-(triphenylphosphine)palladium(o) (2.4mg, 5%) and potassium carbonate (17.4mg, 0.13 mmol) in the mixture of 2mL of 1,4-dioxane and 0.5mL of water was heated at 100°C in the Smith Creator microwave for 800 seconds. The mixture was then diluted with ethyl acetate, washed with water, brine, dried over Anhydrous sodium sulfate, filtered and concentrated to give crude 3-hydroxy intermediate.

Upon oxidation as described in Example 12c with Dess-Martin periodinane (50mg, 0.12mmol), the title compound was obtained (4mg, 15%). LC-MS m/z 627.2 (M^+), 2.49 min.

Example 29

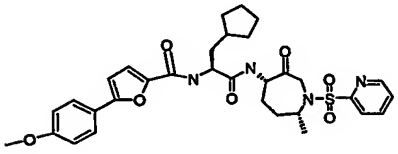
Preparation of 29: 5-(4-fluoro-phenyl)-furan-2-carboxylic acid {(S)-2-cyclopentyl-1-[(4S, 7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide



Following the general procedure described in Example 28b, the coupling of 5-bromo-furan-2-carboxylic acid {(S)-2-cyclopentyl-1-[(4S, 7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide (Example 28a, 25mg, 0.04mmol) with 4-fluorophenylboronic acid (6.4mg, 0.05mmol), followed by oxidation with Dess-Martin periodinane (50mg, 0.12mmol), the title compound was obtained (6.2mg, 24%). LC-MS m/z 611.2(M^+), 2.42min.

Example 30

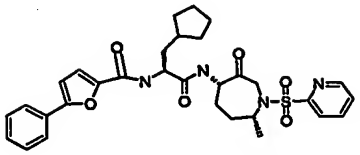
Preparation of 30: 5-(4-methoxy-phenyl)-furan-2-carboxylic acid {(S)-2-cyclopentyl-1-[(4S, 7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide



Following the general procedure described in Example 28b, the coupling of 5-bromo-furan-2-carboxylic acid {(S)-2-cyclopentyl-1-[(4S, 7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide (Example 28a, 25mg, 0.04mmol) with 4-methoxyphenylboronic acid (7.0mg, 0.05mmol), followed by oxidation with Dess-Martin periodinane (50mg, 0.12mmol), the title compound was obtained (18mg, 69%). LC-MS m/z 623.4(M^+), 2.42min.

Example 31

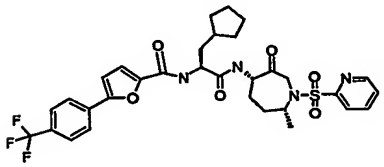
Preparation of 31: 5-phenyl-furan-2-carboxylic acid {(S)-2-cyclopentyl-1-[(4S, 7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide



Following the general procedure described in Example 28b, the coupling of 5-bromo-furan-2-carboxylic acid {(S)-2-cyclopentyl-1-[(4S, 7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide (Example 28a, 25mg, 0.04mmol) with phenylboronic acid (5.6mg, 0.05mmol), followed by oxidation with Dess-Martin periodinane (50mg, 0.12mmol), the title compound was obtained (10mg, 42%). LC-MS m/z 593.2(M^+), 2.40 min.

Example 32

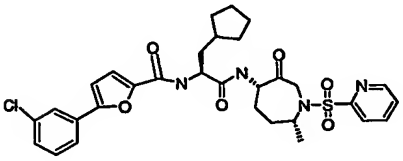
Preparation of 32: 5-(4-trifluoromethyl-phenyl)-furan-2-carboxylic acid {(S)-2-cyclopentyl-1-[(4S, 7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide



Following the general procedure described in Example 28b, the coupling of 5-bromo-furan-2-carboxylic acid {(S)-2-cyclopentyl-1-[(4S, 7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide (Example 28a, 25mg, 0.04mmol) with 4-trifluoromethyl-phenylboronic acid (8.7mg, 0.05mmol), followed by oxidation with Dess-Martin periodinane (50mg, 0.12mmol), the title compound was obtained (15mg, 56%). LC-MS m/z 661.2(M^+), 2.59 min.

Example 33

Preparation of 33: 5-(3-chloro-phenyl)-furan-2-carboxylic acid {(S)-2-cyclopentyl-1-[(4S, 7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide

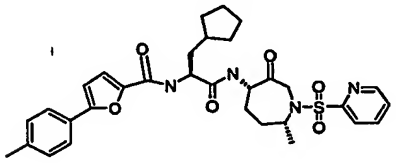


Following the general procedure described in Example 28b, the coupling of 5-bromo-furan-2-carboxylic acid {(S)-2-cyclopentyl-1-[(4S, 7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide (Example 28a, 25mg, 0.04mmol) with 3-chloro-phenylboronic acid (7.2mg, 0.05mmol), followed by oxidation with Dess-Martin periodinane

(23mg, 0.05mmol), the title compound was obtained (7mg, 28%). LC-MS m/z 627.2(M^+), 2.59min

Example 34

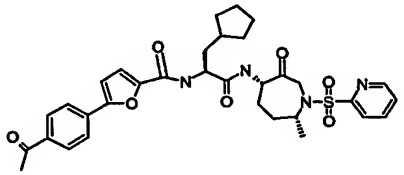
Preparation of 34: 5-(4-methylphenyl)furan-2-carboxylic acid {(S)-2-cyclopentyl-1-[(4S, 7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide



Following the general procedure described in Example 28b, the coupling of 5-bromofuran-2-carboxylic acid {(S)-2-cyclopentyl-1-[(4S, 7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide (Example 28a, 25mg, 0.04mmol) with p-toylboronic acid (6.3mg, 0.05mmol), followed by oxidation with Dess-Martin periodinane (48mg, 0.11mmol), the title compound was obtained (6.2mg, 25%). LC-MS m/z 607.4(M^+), 2.59 min.

Example 35

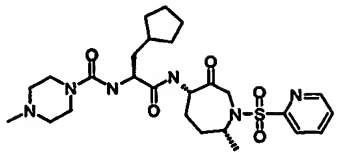
Preparation of 35: 5-(4-acetyl-phenyl)-furan-2-carboxylic acid {(S)-2-cyclopentyl-1-[(4S, 7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide



Following the general procedure described in Example 28b, the coupling of 5-bromo-furan-2-carboxylic acid {(S)-2-cyclopentyl-1-[(4S, 7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide (Example 28a, 25mg, 0.04mmol) with 4-acetyl-phenylboronic acid (7.5mg, 0.05mmol), followed by oxidation with Dess-Martin periodinane (50mg, 0.12mmol), the title compound was obtained (15mg, 59%). LC-MS m/z 635.2(M^+), 2.30 min

Example 36

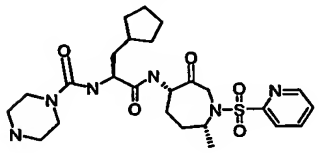
Preparation of 36: 4-Methyl-piperazine-1-carboxylic acid {(S)-2-cyclopentyl-1-[(4S, 7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide



The mixture (S)-2-amino-3-cyclopentyl-N-[(3S, 4S, 7R)-3-hydroxy-7-methyl-1-(pyridine-2-sulfonyl)-azepan-4-yl]-propionamide HCl salt (Example 12b, 150mg, 0.33mmol), 4-methyl-piperazine-1-carbonyl chloride (66mg, 0.33mmol) and 0.5mL of pyridine in 2 mL of dichloromethane was stirred at room temperature for 18 hours. The mixture was then diluted with dichloromethane, washed with water, brine, dried over Anhydrous sodium sulfate, filtered and concentrated to give the crude 3-hydroxy intermediate (117mg). Upon oxidation as described in Example 12c with Dess-Martin reagent (121mg, 0.29mmol), the title compound was obtained (50mg, 43%). LC-MS m/z 549.2 (M^+), 1.46 min.

Example 37

Preparation of 37c: Piperazine-1-carboxylic acid {(S)-2-cyclopentyl-1-[(4S, 7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide



37a.) 4-(1-Imidazol-1-yl-methanoyl)-piperazine-1-carboxylic acid tert-butyl ester

The mixture of piperazine-1-carboxylic acid tert-butyl ester (2.0g, 10.7mmol) and 1,1-di-imidazol-1-yl-methanone (1.9g, 11.8mmol) in 40 mL of tetrohydrofuran was heated to 60°C for 18 hr. The mixture was concentrated and purified via silica gel column chromatography (ethyl acetate 100%) to provide the title compound (3.9g, 100%). ^1H NMR (400Hz, $CDCl_3$): δ 7.90 (s, 1H), 7.22 (s, 1H), 7.14 (s, 1H), 3.61 (t, 4H), 3.55 (t, 4H), 1.50 (s, 9H).

37b.) 4-(1-Imidazol-1-yl-methanoyl)-piperazine-1-carboxylic acid tert-butyl ester methyl iodide salt

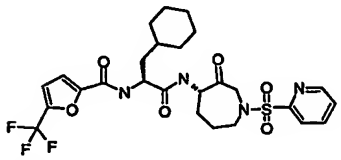
The mixture of 4-(1-Imidazol-1-yl-methanoyl)-piperazine-1-carboxylic acid tert-butyl ester (3.9g, 10.7mmol) and iodomethane (2.67mL, 42.8mmol) in 20 mL of acetonitrile was stirred at room temperature for 18 hr. The mixture was concentrated and the residue was triturated with diethyl ether and hexanes to give the crude material which was used directly in the next step without further purification.

37c.) Piperazine-1-carboxylic acid {(S)-2-cyclopentyl-1-[(4S, 7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide

The mixture of (S)-2-amino-3-cyclopentyl-N-[(3S, 4S, 7R)-3-hydroxy-7-methyl-1-(pyridine-2-sulfonyl)-azepan-4-yl]-propionamide HCl salt (Example 12b, 150mg, 0.33mmol), 4-(1-imidazol-1-yl-methanoyl)-piperazine-1-carboxylic acid tert-butyl ester methyl iodide salt (139mg, 0.33mmol) and triethylamine was heated at 70°C for 10min in the Smithcreator microwave to give the 3-hydroxy intermediate. Upon oxidation with Dess-Martin periodinane (182mg, 0.43mmol) followed by removal of the tert-butoxycarbonyl protecting group with 4N HCl the title compound was obtained (50mg, 28%). LC-MS m/z 535.2 (M^+), 1.44 min.

Example 38

Preparation of 38h: 5-Trifluoromethyl-furan-2-carboxylic acid {(S)-2-cyclohexyl-1-[(s)-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide



38a.) (S)-(R)-1-Oxiranyl-prop-2-en-1-ol

To a mixture of 4A molecular sieves (20g) in 500 mL of dichloromethane at -30°C, was added titanium (IV) isopropoxide (17.7mL, 59.4mmol), followed by diisopropyl D-tartrate (16.4mL, 77.3mmol). The mixture was stirred at –30°C for 30 min. 1,4-pentadien-3-ol (50g, 0.59mol) was added, followed by cumene hydroperoxide (153mL, 0.92mol). After standing at –15°C for 72 hr, 300 mL of diethyl ether and 50 mL of saturated aqueous Anhydrous sodium sulfate were added. The resulting mixture was stirred for 3.5 hours at room temperature, then filtered through celite. The organic phase was separated and concentrated. Column chromatography (5% diethyl ether /95% hextan to 50% diethyl ether /50% hexane) provided the crude title compound (56g), which was used in next step without further purification.

38b.) 2-((R)-(S)-1-Oxiranyl-allyl)-isoindole-1,3-dione

The mixture of (S)-(R)-1-Oxiranyl-prop-2-en-1-ol (50g, 0.5mol), triphenylphosphine (196g, 0.75mol) and phthalimide (110g, 0.75mmol) in 300 mL of toluene was cooled to 0°C where diisopropyl azodicarboxylate (147mL 0.75mol) in 100mL of toluene was added dropwise. The resulting mixture was allowed to warm to ambient temperature and stirred for 18 hours. After standing at –15°C for 60 min, the mixture was filtered and washed with toluene. The filtrate was washed with aqueous 1N NaOH (2x), water, then concentrated. Flash chromatography of the residue (20% diethyl ether /80% hexanes), followed by recrystallization from methanol provided the desired product (41g, 36% two steps). ^{1}H NMR (400Hz, DMSO-

d6): δ 7.87-7.93 (m, 4H), 6.05-6.13 (m, 1H), 5.37-5.34 (m, 2H), 4.40-4.43 (m, 1H), 3.59-3.62 (m, 1H), 2.51-2.92 (m, 2H).

38c.) Pyridine-2-sulfonic acid allyl-[(2S, 3S)-3-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-2-hydroxy-pent-4-enyl]-amide

To a mixture of 2-((R)-(S)-1-oxiranyl-allyl)-isoindole-1,3-dione (30g, 132mmol) and pyridine-2-sulfonic acid allylamide (26g, 132mmol) in 300mL of isopropanol at room temperature, was added 1,8-diazabicyclo[5.4.0]undec-7-ene (1.97mL, 13.2mmol). The mixture was heated to reflux for 18 hours. The mixture was then cooled to ambient temperature, diluted with dichloromethane, washed with aqueous 1N HCl, water, and brine. The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to give the crude material which was used in the next step without further purification.

38d.) 2-[(3S, 4S)-3-Hydroxy-1-(pyridine-2-sulfonyl)-2,3,4,7-tetrahydro-1H-azepin-4-yl]-isoindole-1,3-dione

The mixture of pyridine-2-sulfonic acid allyl-[(2S, 3S)-3-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-2-hydroxy-pent-4-enyl]-amide (53g, 12c4mmol) in 700mL of 1,2-dichloroethane was degassed for 5 min. Grubbs reagent (5.27g, 6.21mmol) was then added. The mixture was heated to 70°C for 18 hours. The mixture was cooled to room temperature and filtered. The solid was washed with ethyl acetate and dried to yield the title compound (22g, 44%). ^{1}H NMR (400Hz, DMSO-d6): δ 8.78 (s, 1H), 8.13 (t, 1H), 7.96 (d, 1H), 7.85-7.89 (m, 4H), 7.73(m, 1H), 5.67-5.74 (m, 2H), 5.51 (m, 1H), 4.93-4.95 (m, 1H), 4.23-4.25 (m, 1H), 3.95 (m, 2H), 3.5980-3.83 (m, 1H), 3.36-3.39 (m, 1H).

38e.) 2-[(3S, 4S)-3-Hydroxy-1-(pyridine-2-sulfonyl)-azepan-4-yl]-isoindole-1,3-dione

To the mixture of 2-[(3S, 4S)-3-hydroxy-1-(pyridine-2-sulfonyl)-2,3,4,7-tetrahydro-1H-azepin-4-yl]-isoindole-1,3-dione (5g, 12c.5mmol) in 80mL of N,N-dimethylformamide and 20mL of ethanol was bubbled argon for 5 min, followed by addition of palladium (10 wt % on activated carbon, 2.5g). The mixture was hydrogenated on a Parr hydrogenation apparatus at 50°C for 2 hours and at room temperature for 16 hours. The mixture was filtered through celite and the filtrate concentrated to give the desired product (4.6g, 91%). LC-MS m/z 402.2(M^+), 1.62min

38f.) (3S, 4S)-4-Amino-1-(pyridine-2-sulfonyl)-azepan-3-ol

To a suspension of 2-[(3S, 4S)-3-hydroxy-1-(pyridine-2-sulfonyl)-azepan-4-yl]-isoindole-1,3-dione (29g, 72mmol) in 500mL of ethanol, hydrazine (8.8mL, 281mmol) was added. The mixture was heated at reflux for 2 hours. After cooling, the mixture was filtered and the filtrate concentrated. The residue was diluted with dichloromethane, washed with aqueous 10% Na_2CO_3, water, and brine. The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to give desired product (15g, 76%). LC-MS m/z 272.0(M^+), 0.75min..

38g.) (S)-2-Amino-3-cyclohexyl-N-[(3S, 4S)-3-hydroxy-1-(pyridine-2-sulfonyl)-azepan-4-yl]-propionamide HCl salt

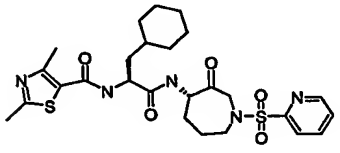
Following the procedure of Example 1p, (S)-2-*tert*-Butoxycarbonylamino-3-cyclohexyl-propionic acid (5.58g, 20.6mmol) and (3S, 4S)-4-Amino-1-(pyridine-2-sulfonyl)-azepan-3-ol, (Example 38f, 5.07g, 18.7 mmol) were reacted, followed by deprotection with 4N HCl in 1,4-dioxane to give the title product. LC-MS m/z 425.2 (M^+), 1.33 min.

38h.) 5-Trifluoromethyl-furan-2-carboxylic acid {(S)-2-cyclohexyl-1-[(s)-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide

Following the general procedure described in Example 12c, (S)-2-amino-3-cyclohexyl-N-[(3S, 4S)-3-hydroxy-1-(pyridine-2-sulfonyl)-azepan-4-yl]-propionamide HCl salt (150mg, 0.33 mmol) was coupled with 5-trifluoromethyl-furan-2-carboxylic acid (72mg, 0.40mmol), followed by oxidation with Dess-Martin periodinane (182mg, 0.43mmol) to give the title compound (17mg, 6%). LC-MS m/z 585.2 (M^+), 2.34 min.

Example 39

Preparation of 39: 2,4-Dimethyl-thiazole-5-carboxylic acid {(S)-2-cyclohexyl-1-[(s)-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide

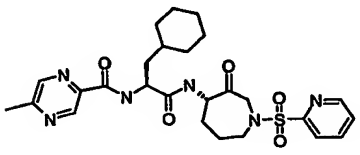


Following the general procedure described in Example 12c, (S)-2-amino-3-cyclohexyl-N-[(3S, 4S)-3-hydroxy-1-(pyridine-2-sulfonyl)-azepan-4-yl]-propionamide HCl salt (Example 38g, 150 mg, 0.33 mmol) was coupled with 2,4-dimethyl-thiazole-5-carboxylic acid (63mg, 0.40mmol), followed by oxidation with Dess-Martin

periodinane (182mg, 0.43mmol) to give the title compound (88mg, 48%). LC-MS m/z 562.0 (M^+), 2.09 min.

Example 40

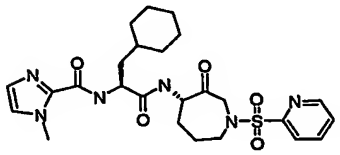
Preparation of 40: 5-Methyl-pyrazine-2-carboxylic acid {(S)-2-cyclohexyl-1-[(s)-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide



Following the general procedure described in Example 12c, (S)-2-amino-3-cyclohexyl-N-[(3S, 4S)-3-hydroxy-1-(pyridine-2-sulfonyl)-azepan-4-yl]-propionamide HCl salt (Example 38g, 150 mg, 0.33 mmol) was coupled with 5-methyl-pyrazine-2-carboxylic acid (55mg, 0.40mmol), followed by oxidation with Dess-Martin periodinane (182mg, 0.43mmol) to give the title compound (62mg, 35%). LC-MS m/z 543.2 (M^+), 2.07 min.

Example 41

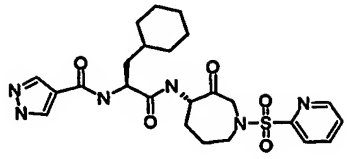
Preparation of 41: 1-Methyl-1H-imidazole-2-carboxylic acid {(S)-2-cyclohexyl-1-[(s)-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide



Following the general procedure described in Example 12c, (S)-2-amino-3-cyclohexyl-N-[(3S, 4S)-3-hydroxy-1-(pyridine-2-sulfonyl)-azepan-4-yl]-propionamide HCl salt (Example 38g, 150 mg, 0.33 mmol) was coupled with 1-methyl-1H-imidazole-2-carboxylic acid (50mg, 0.40mmol), followed by oxidation with Dess-Martin periodinane (182mg, 0.43mmol) to give the title compound (70mg, 40%). LC-MS m/z 531.0 (M^+).

Example 42

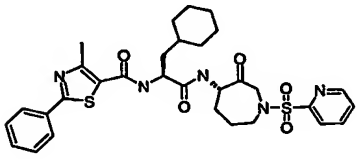
Preparation of 42: 1H-Pyrazole-4-carboxylic acid {(S)-2-cyclohexyl-1-[(s)-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide



Following the general procedure described in Example 12c, (S)-2-amino-3-cyclohexyl-N-[(3S, 4S)-3-hydroxy-1-(pyridine-2-sulfonyl)-azepan-4-yl]-propionamide HCl salt (Example 38g, 165mg, 0.36 mmol) was coupled with pyrazole-1,4-dicarboxylic acid-1-tert-butyl ester (Example 18a, 77mg, 0.36mmol), followed by removal of the tert-butoxycarbonyl protecting group with 4N HCl. Oxidation with Dess-Martin periodinane (182mg, 0.43mmol) gave the title compound (40mg, 21%). LC-MS m/z 517.2 (M^+), 1.72 min.

Example 43

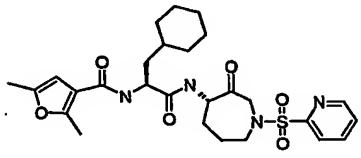
Preparation of 43: 4-Methyl-2-phenyl-thiazole-5-carboxylic acid {(S)-2-cyclohexyl-1-[(s)-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide



Following the general procedure described in Example 12c, (S)-2-amino-3-cyclohexyl-N-[(3S, 4S)-3-hydroxy-1-(pyridine-2-sulfonyl)-azepan-4-yl]-propionamide HCl salt (Example 38g, 150 mg, 0.33 mmol) was coupled with 4-methyl-2-phenyl-thiazole-5-carboxylic acid (88mg, 0.40mmol), followed by oxidation with Dess-Martin periodinane (182mg, 0.43mmol) to give the title compound (117mg, 57%). LC-MS m/z 624.2 (M^+), 2.50 min.

Example 44

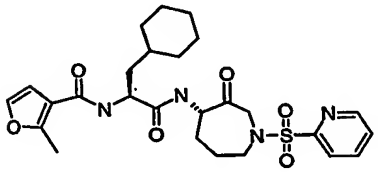
Preparation of 44: 2,5-Dimethyl-furan-3-carboxylic acid {(S)-2-cyclohexyl-1-[(S)-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide



Following the general procedure described in Example 12c, (S)-2-amino-3-cyclohexyl-N-[(3S, 4S)-3-hydroxy-1-(pyridine-2-sulfonyl)-azepan-4-yl]-propionamide HCl salt (Example 38g, 150 mg, 0.33 mmol) was coupled with 2,5-dimethyl-furan-3-carboxylic acid (56mg, 0.40mmol), followed by oxidation with Dess-Martin periodinane (182mg, 0.43mmol) to give the title compound (42mg, 23%). LC-MS m/z 545.0 (M^+), 2.27 min.

Example 45

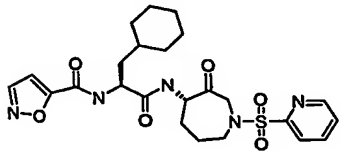
Preparation of 45: 2-Methyl-furan-3-carboxylic acid {(S)-2-cyclohexyl-1-[(S)-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide



Following the general procedure described in Example 12c, (S)-2-amino-3-cyclohexyl-N-[(3S, 4S)-3-hydroxy-1-(pyridine-2-sulfonyl)-azepan-4-yl]-propionamide HCl salt (Example 38g, 150 mg, 0.33 mmol) was coupled with 2-methyl-furan-3-carboxylic acid (50mg, 0.40mmol), followed by oxidation with Dess-Martin periodinane (182mg, 0.43mmol) to give the title compound (39mg, 22%). LC-MS m/z 531.0 (M^+), 2.13 min.

Example 46

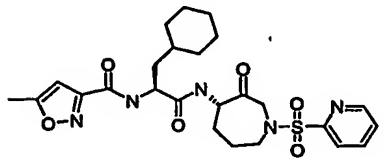
Preparation of 46: Isoxazole-5-carboxylic acid {(S)-2-cyclohexyl-1-[(S)-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide



Following the general procedure described in Example 12c, (S)-2-amino-3-cyclohexyl-N-[(3S, 4S)-3-hydroxy-1-(pyridine-2-sulfonyl)-azepan-4-yl]-propionamide HCl salt (Example 38g, 100 mg, 0.22 mmol) was coupled with isoxazole-5-carboxylic acid (25mg, 0.22mmol), followed by oxidation with Dess-Martin periodinane (182mg, 0.43mmol) to give the title compound (40mg, 35%). LC-MS m/z 518.2 (M^+), 1.94 min.

Example 47

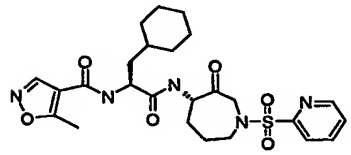
Preparation of 47: 5-Methyl-isoxazole-3-carboxylic acid {(S)-2-cyclohexyl-1-[(S)-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide



Following the general procedure described in Example 12c, (S)-2-amino-3-cyclohexyl-N-[(3S, 4S)-3-hydroxy-1-(pyridine-2-sulfonyl)-azepan-4-yl]-propionamide HCl salt (Example 38g, 100 mg, 0.22 mmol) was coupled with 5-methyl-isoxazole-3-carboxylic acid (28mg, 0.22mmol), followed by oxidation with Dess-Martin periodinane (182mg, 0.43mmol) to give the title compound (53mg, 45%). LC-MS m/z 531.8 (M^+), 2.14 min.

Example 48

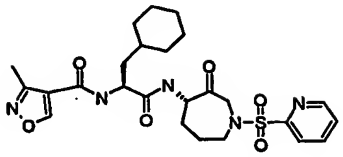
Preparation of 48: 5-Methyl-isoxazole-4-carboxylic acid {(S)-2-cyclohexyl-1-[(S)-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide



Following the general procedure described in Example 12c, (S)-2-amino-3-cyclohexyl-N-[(3S, 4S)-3-hydroxy-1-(pyridine-2-sulfonyl)-azepan-4-yl]-propionamide HCl salt (Example 38g, 100 mg, 0.22 mmol) was coupled with 5-methyl-isoxazole-4-carboxylic acid (28mg, 0.22mmol), followed by oxidation with Dess-Martin periodinane (121mg, 0.29mmol) to give the title compound (26mg, 22%). LC-MS m/z 532.0 (M^+), 2.04 min.

Example 49

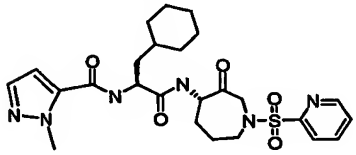
Preparation of 49: 3-Methyl-isoxazole-4-carboxylic acid {(S)-2-cyclohexyl-1-[(S)-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide



Following the general procedure described in Example 12c, (S)-2-amino-3-cyclohexyl-N-[(3S, 4S)-3-hydroxy-1-(pyridine-2-sulfonyl)-azepan-4-yl]-propionamide HCl salt (Example 38g, 100 mg, 0.22 mmol) was coupled with 3-methyl-isoxazole-4-carboxylic acid (28mg, 0.22mmol), followed by oxidation with Dess-Martin periodinane (121mg, 0.29mmol) to give the title compound (16mg, 14%). LC-MS m/z 532.0 (M^+), 2.04 min.

Example 50

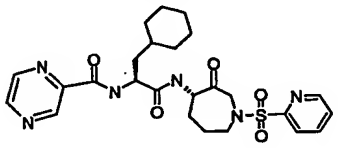
Preparation of 50: 2-Methyl-2H-pyrazole-3-carboxylic acid {(S)-2-cyclohexyl-1-[(S)-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide



Following the general procedure described in Example 12c, (S)-2-amino-3-cyclohexyl-N-[(3S, 4S)-3-hydroxy-1-(pyridine-2-sulfonyl)-azepan-4-yl]-propionamide HCl salt (Example 38g, 100 mg, 0.22 mmol) was coupled with 2-methyl-2H-pyrazole-3-carboxylic acid (28mg, 0.22mmol), followed by oxidation with Dess-Martin periodinane (121mg, 0.29mmol) to give the title compound (20mg, 16%). LC-MS m/z 531.2 (M^+), 1.97 min.

Example 51

Preparation of 51: Pyrazine-2-carboxylic acid {(S)-2-cyclohexyl-1-[(S)-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide

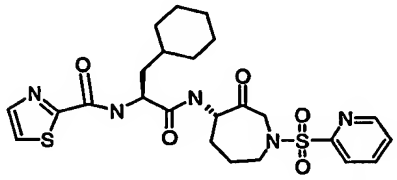


Following the general procedure described in Example 12c, (S)-2-amino-3-cyclohexyl-N-[(3S, 4S)-3-hydroxy-1-(pyridine-2-sulfonyl)-azepan-4-yl]-propionamide

HCl salt (Example 38g, 100 mg, 0.22 mmol) was coupled with pyrazine-2-carboxylic acid (27mg, 0.22mmol), followed by oxidation with Dess-Martin periodinane (121mg, 0.29mmol) to give the title compound (15mg, 13%). LC-MS m/z 529.2 (M^+), 2.02 min.

Example 52

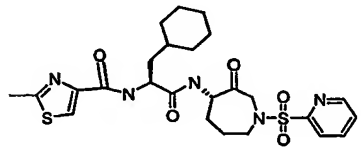
Preparation of 52: Thiazole-2-carboxylic acid {(S)-2-cyclohexyl-1-[(S)-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide



Following the general procedure described in Example 12c, (S)-2-amino-3-cyclohexyl-N-[(3S, 4S)-3-hydroxy-1-(pyridine-2-sulfonyl)-azepan-4-yl]-propionamide HCl salt (Example 38g, 94 mg, 0.20 mmol) was coupled with thiazole-2-carboxylic acid (Example 16a, 26mg, 0.20mmol), followed by oxidation with Dess-Martin periodinane (121mg, 0.29mmol) to give the title compound (45mg, 28%). LC-MS m/z 534.0 (M^+), 2.10 min.

Example 53

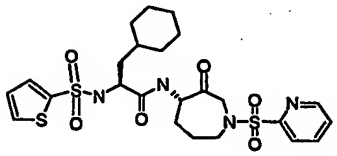
Preparation of 53: 2-Methyl-thiazole-4-carboxylic acid {(S)-2-cyclohexyl-1-[(S)-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide



Following the general procedure described in Example 12c, (S)-2-amino-3-cyclohexyl-N-[(3S, 4S)-3-hydroxy-1-(pyridine-2-sulfonyl)-azepan-4-yl]-propionamide HCl salt (Example 38g, 100 mg, 0.22 mmol) was coupled with 2-methyl-thiazole-4-carboxylic acid (32mg, 0.22mmol), followed by oxidation with Dess-Martin periodinane (121mg, 0.29mmol) to give the title compound (34mg, 28%). LC-MS m/z 548.0 (M^+), 2.10 min.

Example 54

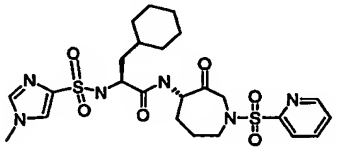
Preparation of 54: (S)-3-Cyclohexyl-N-[(S)-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-yl]-2-(thiophene-2-sulfonylamino)-propionamide



The mixture of (S)-2-amino-3-cyclohexyl-N-[(3S, 4S)-3-hydroxy-1-(pyridine-2-sulfonyl)-azepan-4-yl]-propionamide HCl salt (Example 38g, 100 mg, 0.22 mmol), thiophene-2-sulfonyl chloride (40mg, 0.22mmol) and triethyl amine (0.15mL, 1.1mmol) in 1 mL of dichloromethane was stirred at room temperature for 18 hours. The mixture was then diluted with ethyl acetate, washed with water and brine and dried over anhydrous sodium sulfate, filtered and concentrated to give the crude 3-hydroxy intermediate. Upon oxidation with Dess-Martin periodinane (121mg, 0.29mmol) the title compound was obtained (95mg, 76%). LC-MS m/z 569.0 (M^+), 2.15 min.

Example 55

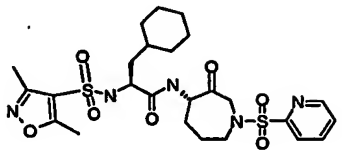
Preparation of 55: (S)-3-Cyclohexyl-2-(1-methyl-1H-imdiazole-4-sulfonylamino)-N-[(S)-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-yl]-propionamide



Following the general procedure described in Example 54, (S)-2-amino-3-cyclohexyl-N-[(3S, 4S)-3-hydroxy-1-(pyridine-2-sulfonyl)-azepan-4-yl]-propionamide HCl salt (Example 38g, 100 mg, 0.22 mmol) was coupled with 1-methyl-1H-imdiazole-4-sulfonyl chloride (20mg, 0.11mmol), followed by oxidation with Dess-Martin periodinane (121mg, 0.29mmol) to give the title compound (19mg, 30%). LC-MS m/z 567.4 (M^+), 1.77 min.

Example 56

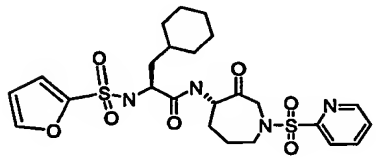
Preparation of 56: (S)-3-Cyclohexyl-2-(3,5-dimethyl-isoxazole-4-sulfonylamino)-N-[(S)-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-yl]-propionamide



Following the general procedure described in Example 54, (S)-2-amino-3-cyclohexyl-N-[(3S, 4S)-3-hydroxy-1-(pyridine-2-sulfonyl)-azepan-4-yl]-propionamide HCl salt (Example 38g, 100 mg, 0.22 mmol) was coupled with 3,5-dimethyl-isoxazole-4-sulfonyl chloride (43mg, 0.22mmol), followed by oxidation with Dess-Martin periodinane (121mg, 0.29mmol) to give the title compound (46mg, 36%). LC-MS m/z 582.4 (M^+), 2.08 min.

Example 57

Preparation of 57b: (S)-3-Cyclohexyl-2-(furan-2-sulfonylamino)-N-[(S)-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-yl]-propionamide



57a.) Furan-2-sulfonyl chloride

To a solution of furan (1.0g, 15mmol) in 10mL of tetrahydrofuran at –78°C, n-butyl lithium (1.6M in hexane, 10mL, 16mmol) was added dropwise. The mixture was stirred at –78°C for 30 min, after which time sulfur dioxide was bubbled through the solution for 5 min. The resulting mixture was then stirred for an additional 1 hour and warmed to ambient temperature. After re-cooling to 0°C, sulphuryl chloride (1.17mL, 14.7mmol) was added and the mixture stirred for 2 hours. The mixture was diluted with ethyl acetate, washed with water and brine, dried over $MgSO_4$, filtered and concentrated to give crude material (1.5g) which was used in the next step without further purification.

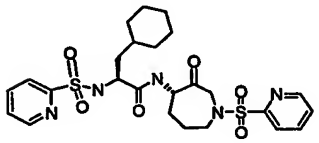
57b.) (S)-3-Cyclohexyl-2-(furan-2-sulfonylamino)-N-[(S)-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-yl]-propionamide

Following the general procedure described in Example 54, (S)-2-amino-3-cyclohexyl-N-[(3S, 4S)-3-hydroxy-1-(pyridine-2-sulfonyl)-azepan-4-yl]-propionamide HCl salt (Example 38g, 150 mg, 0.33 mmol) was coupled with furan-2-sulfonyl

chloride (54mg, 0.33mmol), followed by oxidation with Dess-Martin periodinane (121mg, 0.29mmol) to give the title compound (34mg, 19%). LC-MS m/z 553.2 (M^+), 2.00 min.

Example 58

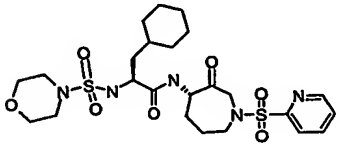
Preparation of 58: (S)-3-Cyclohexyl-N-[(S)-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-yl]-2-(pyridine-2-sulfonylamino)-propionamide



Following the general procedure described in Example 54, (S)-2-amino-3-cyclohexyl-N-[(3S, 4S)-3-hydroxy-1-(pyridine-2-sulfonyl)-azepan-4-yl]-propionamide HCl salt (Example 38g, 100 mg, 0.22 mmol) was coupled with pyridine-2-sulfonyl chloride (39mg, 0.22mmol), followed by oxidation with Dess-Martin periodinane (121mg, 0.29mmol) to give the title compound (19mg, 15%). LC-MS m/z 564.0 (M^+), 1.88 min.

Example 59

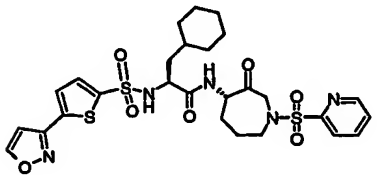
Preparation of 59: (S)-3-Cyclohexyl-2-(morpholine-4-sulfonylamino)-N-[(S)-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-yl]-propionamide



Following the general procedure described in Example 54, (S)-2-amino-3-cyclohexyl-N-[(3S, 4S)-3-hydroxy-1-(pyridine-2-sulfonyl)-azepan-4-yl]-propionamide HCl salt (Example 38g, 100 mg, 0.22 mmol) was coupled with morpholine-4-sulfonyl chloride (prepared from coupling of morpholing with sulphuryl chloride, 41mg, 0.22mmol), followed by oxidation with Dess-Martin periodinane (121mg, 0.29mmol) to give the title compound (7mg, 6%). LC-MS m/z 572.0 (M^+).

Example 60

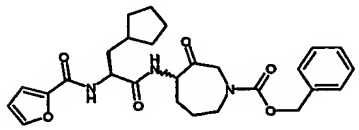
Preparation of 60: (S)-3-Cyclohexyl-2-(5-isoxazol-3-yl-thiophene-2-sulfonylamino)-N-[(S)-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-yl]-propionamide



Following the general procedure described in Example 54, (S)-2-amino-3-cyclohexyl-N-[(3S, 4S)-3-hydroxy-1-(pyridine-2-sulfonyl)-azepan-4-yl]-propionamide HCl salt (Example 38g, 100 mg, 0.22 mmol) was coupled with 5-isoxazol-3-yl-thiophene-2-sulfonyl chloride (55mg, 0.22mmol), followed by oxidation with Dess-Martin periodinane (121mg, 0.29mmol) to give the title compound (38mg, 27%). LC-MS m/z 636.2 (M^+), 2.12 min.

Example 61

Preparation of 61: 4-{(S)-3-Cyclopentyl-2-[(1-furan-2-yl-methanoyl)-amino]-propanoylamino}-3-oxo-azepane-1-carboxylic acid benzyl ester (first diastereomer eluted)



61a.) Allyl-pent-4-enyl-carbamic acid benzyl ester

To a suspension of NaH (1.83 g, 76.33 mmol of 90% NaH) in DMF was added benzyl allyl-carbamic acid benzyl ester (7.3 g, 38.2 mmol) in a dropwise fashion. The mixture was stirred at room temperature for approximately 10 minutes whereupon 5-bromo-1-pentene (6.78 mL, 57.24 mmol) was added in a dropwise fashion. The reaction was heated to 40°C for approximately 4 hours whereupon the reaction was partitioned between dichloromethane and water. The organic layer was washed with water (2x's), brine, dried ($MgSO_4$), filtered and concentrated. Column chromatography of the residue (10% ethyl acetate:hexanes) provided 10.3 grams of the title compound as an oil: MS(EI) 260 ($M+H^+$).

61b.) 2,3,4,7-Tetrahydro-azepine-1-carboxylic acid benzyl ester

To a solution of compound of Example 1a (50 g) in dichloromethane was added bis(tricyclohexylphosphine)benzylidine ruthenium (IV) dichloride (5.0 g). The reaction was heated to reflux until complete as determined by TLC analysis. The reaction was concentrated

in vacuo. Column chromatography of the residue (50% dichloromethane:hexanes) gave 35 g of the title compound: MS(EI) 232 ($M+H^+$).

61c.) 8-Oxa-3-aza-bicyclo[5.1.0]octane-3-carboxylic acid benzyl ester

To a solution of the compound of Example 1b (35 g, 1.5 mol) in CH_2Cl_2 was added *m*-CPBA (78 g, 0.45 mol). The mixture was stirred overnight at room temperature whereupon it was filtered to remove the solids. The filtrate was washed with water and saturated $NaHCO_3$ (several times). The organic layer was dried ($MgSO_4$), filtered and concentrated to give 35 g of the title compound which was of sufficient purity to use in the next step: MS(EI) 248 ($M+H^+$), 270 ($M+Na^+$).

61d.) 4-azido-3-hydroxy-azepane-1-carboxylic acid benzyl ester

To a solution of the epoxide from Example 1c (2.0 g, 8.1 mmol) in methanol:water (8:1 solution) was added NH_4Cl (1.29 g, 24.3 mmol) and sodium azide (1.58 g, 24.30 mmol). The reaction was heated to 40°C until complete consumption of the starting epoxide was observed by TLC analysis. The majority of the solvent was removed *in vacuo* and the remaining solution was partitioned between ethyl acetate and pH 4 buffer. The organic layer was washed with sat. $NaHCO_3$, water, brine dried ($MgSO_4$), filtered and concentrated. Column chromatography (20% ethyl acetate:hexanes) of the residue provided 1.3 g of the title compound: MS(EI) 291 ($M+H^+$) plus 0.14 g of trans-4-hydroxy-3-azido-hexahydro-1H-azepine

61e.) 4-Amino-3-hydroxy-azepane-1-carboxylic acid benzyl ester

To a solution of the azido alcohol of Example 1d (1.1 g, 3.79 mmol) in methanol was added triethylamine (1.5 mL, 11.37 mmol) and 1,3-propanedithiol (1.1 mL, 11.37 mL). The reaction was stirred until complete consumption of the starting material was observed by TLC analysis whereupon the reaction was concentrated *in vacuo*. Column chromatography of the residue (20% methanol:dichloromethane) provided 0.72 g of the title compound: MS(EI) 265 ($M+H^+$).

61f.) 4-((S)-2-*tert*-Butoxycarbonylamino-3-cyclopentyl-propanoylamino)-3-hydroxy-azepane-1-carboxylic acid benzyl ester

To a mixture of the hydrochloride salt of 4-amino-3-hydroxy-azepane-1-carboxylic acid benzyl ester (Example 61e, 1.17 g, 3.89 mmol), (S)-2-*tert*-butoxycarbonylamino-3-cyclopentylpropionic acid (1.0 g, 3.89 mmol),and 4-methylmorpholine (1.985 g, 19.45 mmol) stirring in DMF (40 mL) was added HBTU (1.915 g, 5.05 mmol). The resulting mixture was stirred under argon at room temperature for 90 minutes. The reaction was concentrated *in*

vacuo, and the residue was partitioned between ethyl acetate and water. The organic phase was washed with water (3X), brine (1X), dried over anhydrous sodium sulfate, filtered and evaporated to give the crude product which was flash chromatographed on silica gel (70 g) eluted with 0-4% methanol in methylene chloride to give the title compound (a mixture of diastereomers) as a white foam. LC-MS $M+H^+ = 504$.

61g.) 4-((S)-2-Amino-3-cyclopentyl-propanoylamino)-3-hydroxy-azepane-1-carboxylic acid benzyl ester

4-((S)-2-*tert*-Butoxycarbonylamino-3-cyclopentyl-propanoylamino)-3-hydroxy-azepane-1-carboxylic acid benzyl ester (Example 61f, 1.81 g, 3.6 mmol) was dissolved in methanol (55 mL), and treated with HCL in dioxane (4.0 M, 13.5 mL). The mixture was stirred under argon at room temperature for 6 hours. The reaction was concentrated *in vacuo*. The residue was mixed with toluene and concentrated *in vacuo* (2X). The residue was triturated with ether (2X), and the residue dried *in vacuo* overnight to give the crude title product (a mixture of diastereomers) as a white foam which was used without further purification.h LC-MS $M+H^+ = 404$.

61h.) 4-{(S)-3-Cyclopentyl-2-[(1-furan-2-yl-methanoyl)-amino]-propanoylamino}-3-hydroxy-azepane-1-carboxylic acid benzyl ester

To a mixture of 4-((S)-2-amino-3-cyclopentyl-propanoylamino)-3-hydroxy-azepane-1-carboxylic acid benzyl ester (Example 61g,1.6 g, 3.64 mmol), 2-furoic acid (0.416 g, 3.64 mmol),and 4-methylmorpholine (1.84 g, 18.2 mmol) stirring in DMF (46 mL) was added HBTU (1.79 g, 4.73 mmol). The resulting mixture was stirred under argon at room temperature for 1 hour. The reaction was concentrated *in vacuo*, and the residue partitioned between ethyl acetate and water. The organic phase was washed with water (3X), brine (1X), dried over anhydrous sodium sulfate, filtered and evaporated to give the crude product which was flash chromatographed on silica gel (90 g) eluted with 1-4% methanol in methylene chloride. This material was rechromatographed on silica gel (120 g) eluted with 0-4% methanol in methylene chloride to give the title compound (a mixture of diastereomers) as a white solid. LC-MS $M+H^+ = 498$.

61i.) 4-{(S)-3-Cyclopentyl-2-[(1-furan-2-yl-methanoyl)-amino]-propanoylamino}-3-oxo-azepane-1-carboxylic acid benzyl ester

To a solution of 4-{(S)-3-cyclopentyl-2-[(1-furan-2-yl-methanoyl)-amino]-propanoylamino}-3-hydroxy-azepane-1-carboxylic acid benzyl ester (Example 61h, 103 mg,

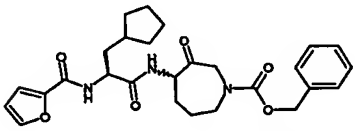
0.207 mmol) stirring under argon in methylene chloride (10 mL) was added Dess-Martin periodinane (132 mg, 0.311 mmol). The mixture was stirred for 1 hour at room temperature. The reaction was worked up by diluting with methylene chloride and washing the organic phase three times with a 1:1 mixture of 10% $NaHCO_3$ and 10% $Na_2S_2O_5$. The organic phase was dried over anhydrous sodium sulfate, filtered and evaporated. The crude product was chromatographed on silica gel (10 g) eluted with 0-4% methanol in methylene chloride to give the title compound as a mixture of diastereomers. LC-MS $M+H^+ = 496$.

61j.) 4-{(S)-3-Cyclopentyl-2-[(1-furan-2-yl-methanoyl)-amino]-propanoylamino}-3-oxo-azepane-1-carboxylic acid benzyl ester (first diastereomer eluted)

The mixture of diastereomers from Example 61i was separated on a preparative R,R Whelk-O column. The first diastereomer eluted was the title compound, a white amorphous solid. mp 72-74°C; LC-MS $M+H^+ = 496$; ^1H NMR (400Hz, $CDCl_3$): δ 7.48 (s, 1H), 7.36-7.41 (m, 5H), 6.94-6.99 (m, 1H), 6.78-6.84 (m, 2H), 6.53 (s, 1H), 5.09-5.28 (m, 2H), 4.22-4.82 (m, 4H), 3.62-3.71 (m, 1H), 1.17-2.67 (m, 16H).

Example 62

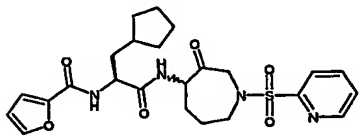
Preparation of 62: 4-{(S)-3-Cyclopentyl-2-[(1-furan-2-yl-methanoyl)-amino]-propanoylamino}-3-oxo-azepane-1-carboxylic acid benzyl ester (second diastereomer eluted)



The mixture of diastereomers from Example 61i was separated on a preparative R,R Whelk-O column. The second diastereomer eluted was the title compound, a white amorphous solid. mp 66-68°C; LC-MS $M+H^+ = 496$; ^1H NMR (400Hz, $CDCl_3$): δ 7.49 (s, 1H), 6.74-7.39 (m, 8H), 6.53 (s, 1H), 4.23-4.28 (m, 6H), 3.59-3.70 (m, 1H), 1.18-2.67 (m, 16H).

Example 63

Preparation of 63b: Furan-2-carboxylic acid {(S)-2-cyclopentyl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]ethyl}-amide (first diastereomer eluted)



63a.) Furan-2-carboxylic acid [(S)-2-cyclopentyl-1-(3-hydroxy-azepan-4-ylcarbamoyl)-ethyl]-amide

4-{(S)-3-Cyclopentyl-2-[(1-furan-2-yl-methanoyl)-amino]-propanoylamino}-3-hydroxy-azepane-1-carboxylic acid benzyl ester (Example 61h, 0.5 g, 1 mmol) was dissolved in methylene chloride (10 mL) and stirred under argon in an ice bath. Trimethylsilyl iodide (0.5 mL, 3.5 mmol)was added dropwise, and the ice bath was removed. After stirring for three hours at room temperature the solvent was removed *in vacuo*. The residue was taken up in ether and extracted three times with 1N HCl. The combined aqueous HCl phases were neutralized with solid sodium carbonate, and extracted with methylene chloride (5X). The combined organic phases were dried over anhydrous sodium sulfate, filtered, and evaporated to give the title compound (a mixture of diastereomers) as a white solid which was used without further purification. LC-MS $M+H^+ = 364$.

63b.) Furan-2-carboxylic acid {(S)-2-cyclopentyl-1-[3-hydroxy-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide

Furan-2-carboxylic acid [(S)-2-cyclopentyl-1-(3-hydroxy-azepan-4-ylcarbamoyl)-ethyl]-amide (Example 63a, 72 mg, 0.2 mmol) was dissolved in methylene chloride (5 mL), and a solution of 10% aqueous sodium bicarbonate (0.84 mL) was added. The mixture was stirred rapidly at room temperature, and pyridine-2-sulfonyl chloride (35.4 mg, 0.2 mmol) was added. After two hours, the reaction was diluted with methylene chloride, and water; and extracted with methylene chloride (3X). The combined organic phases were dried over anhydrous sodium sulfate filtered and evaporated to give the crude product. Flash chromatography on silica gel eluted with 0-4% methanol in methylene chloride gave the title compound as a mixture of diastereomers; C-MS $M+H^+ = 505$.

63c.) Furan-2-carboxylic acid {(S)-2-cyclopentyl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide

Following the procedure of Example 61i, except substituting furan-2-carboxylic acid {(S)-2-cyclopentyl-1-[3-hydroxy-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide (the product of Example 63b) for 4-{(S)-3-cyclopentyl-2-[(1-furan-2-yl-methanoyl)-amino]-propanoylamino}-3-hydroxy-azepane-1-carboxylic acid benzyl ester. gave the title compound as a mixture of diastereomers. LC-MS $M+H^+ = 503$.

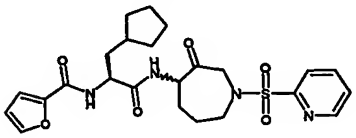
63d.) Furan-2-carboxylic acid {(S)-2-cyclopentyl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide (first diastereomer eluted)

The mixture of diastereomers from Example 63c was separated on a preparative Chiralpak AD column. The first diastereomer eluted was the title compound, a white

amorphous solid. mp 81-84°C; LC-MS M+H$^+$ = 503; ^{1}H NMR (400Hz, $CDCl_3$): δ 8.71 (d, 1H), 7.94-7.99 (m, 2H), 7.50-7.54 (m, 2H), 7.16-7.17 (m, 1H), 7.08-7.09 (m, 1H), 6.77-6.80 (m, 1H), 6.53-6.54 (m, 1H), 5.14-5.17 (m, 1H),4.64-4.76 (m, 2H), 4.11-4.30 (m, 1H), 3.85 (d, 1H), 2.74-2.75 (m, 1H), 1.15-2.25 (m, 15H).

Example 64

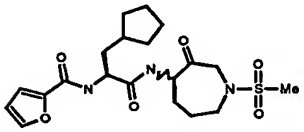
Preparation of 64: Furan-2-carboxylic acid {(S)-2-cyclopentyl-1-[3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]ethyl}-amide (second diastereomer eluted)



The mixture of diastereomers from Example 63c was separated on a preparative Chiralpak AD column. The second diastereomer eluted was the title compound, a white amorphous solid. mp 77-80°C; LC-MS M+H$^+$ = 503; ^{1}H NMR (400Hz, $CDCl_3$): δ 8.71 (d, 1H), 7.93-8.01 (m, 2H), 7.48-7.56 (m, 2H), 7.13-7.14 (m, 1H), 6.96-6.97 (m, 1H), 6.84-6.86 (m, 1H), 6.51-6.52 (m, 1H), 5.14-5.22 (m, 1H),4.64-4.76 (m, 2H), 4.11-4.16 (m, 1H), 3.85 (d, 1H), 2.68-2.75 (m, 1H), 1.19-2.27 (m, 15H).

Example 65

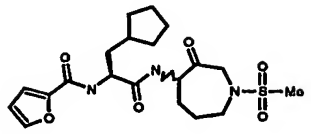
Preparation of 65: Furan-2-carboxylic acid [(S)-2-cyclopentyl-1-(1-methanesulfonyl-3-oxo-azepan-4-ylcarbamoyl)-ethyl]-amide (first diastereomer eluted)



Following the procedure of Example 63 (b-d), except substituting methanesulfonyl chloride for pyridine-2-sulfonyl chloride in step 63b, and separating the diastereomers on a preparative R,R Whelk-O column, gave the title compound as the first diastereomer eluted, an off-white amorphous solid. mp 167-170°C; LC-MS M+H$^+$ = 440; ^{1}H NMR (400Hz, $CDCl_3$): δ 7.48 (s, 1H), 7.15-7.16 (m, 1H), 6.93 (m, 1H), 6.85(m, 1H), 6.51-6.523(m, 1H), 5.14-5.22 (m, 1H),4.52-4.71 (m, 2H), 4.11-4.16 (m, 1H), 3.65 (d, 1H), 2.93 (s, 3H) 1.16-2.93 (m, 16H).

Example 66

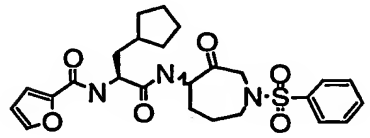
Preparation of 66: Furan-2-carboxylic acid [(S)-2-cyclopentyl-1-(1-methanesulfonyl-3-oxo-azepan-4-ylcarbamoyl)-ethyl]-amide (second diastereomer eluted)



Following the procedure of Example 63 (b-d), except substituting methanesulfonyl chloride for pyridine-2-sulfonyl chloride in step 63b, and separating the diastereomers on a preparative R,R Whelk-O column, gave the title compound as the second diastereomer eluted, an off-white amorphous solid. . mp 158-161°C; LC-MS M+H$^+$ = 440; ^{1}H NMR (400Hz, $CDCl_3$): δ 7.49 (s, 1H), 7.16-7.17 (m, 1H), 7.12-7.13 (m, 1H), 6.75-6.78(m, 1H), 6.52-6.54(m, 1H), 5.14-5.22 (m, 1H), 4.48-4.70 (m, 2H), 4.01-4.06 (m, 1H), 3.68 (d, 1H), 2.92 (s, 3H) 1.15-2.82 (m, 16H).

Example 67

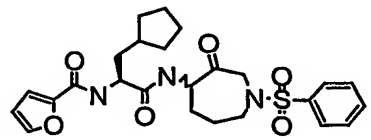
Preparation of 67: Furan-2-carboxylic acid [(S)-1-(1-benzenesulfonyl-3-oxo-azepan-4-ylcarbamoyl)-2-cyclopentyl-ethyl]-amide (first diastereomer eluted)



Following the procedure of Example 63 (b-d), except substituting benzenesulfonyl chloride for pyridine-2-sulfonyl chloride in step 63b, and separating the diastereomers on a preparative R,R Whelk-O column, gave the title compound as the first diastereomer eluted, an off-white amorphous solid. mp 88-90°C; LC-MS M+H$^+$ = 502; ^{1}H NMR (400Hz, $CDCl_3$): δ 7.82 (d, 2H), 7.48-7.66 (m, 4H), 7.13-7.14 (m, 1H), 6.82-6.91 (m, 2H), 6.52-6.53(m, 1H), 5.05-5.09 (m, 1H), 4.59-4.63 (m, 2H), 4.04-4.07 (m, 1H), 3.45 (d, 1H), 1.19-2.51 (m, 16H).

Example 68

Preparation of 68: Furan-2-carboxylic acid [(S)-1-(1-benzenesulfonyl-3-oxo-azepan-4-ylcarbamoyl)-2-cyclopentyl-ethyl]-amide (second diastereomer eluted)

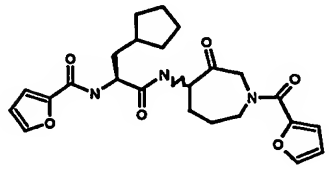


Following the procedure of Example 63 (b-d), except substituting benzenesulfonyl chloride for pyridine-2-sulfonyl chloride in step 63b, and separating the diastereomers on a preparative R,R Whelk-O column, gave the title compound as the second diastereomer eluted, a

white crystalline solid. mp 166-167°C; LC-MS M+H$^+$ = 502; ^{1}H NMR (400Hz, $CDCl_3$): δ 7.80 (d, 2H), 7.50-7.66 (m, 4H), 7.17-7.18 (m, 1H), 7.04 (m, 1H), 6.78 (m, 1H), 6.53-6.54(m, 1H), 5.03-5.08 (m, 1H), 4.50-4.66 (m, 2H), 3.98-4.02 (m, 1H), 3.48 (d, 1H), 1.18-2.56 (m, 16H).

Example 69

Preparation of 69: Furan-2-carboxylic acid {(S)-2-cyclopentyl-1-[1-(1-furan-2-yl-methanoyl)-3-oxo-azepan-4-ylcarbamoyl]-ethyl}-amide (first diastereomer eluted)



69a.) Furan-2-carboxylic acid {(S)-2-cyclopentyl-1-[1-(1-furan-2-yl-methanoyl)-3-hydroxy-azepan-4-ylcarbamoyl]-ethyl}-amide

To a mixture of furan-2-carboxylic acid [(S)-2-cyclopentyl-1-(3-hydroxy-azepan-4-ylcarbamoyl)-ethyl]-amide (Example 63a,70 mg, 0.19 mmol), 2-furoic acid (22.4 mg, 0.19 mmol),and 4-methylmorpholine (0.1 mL, 0.95 mmol) stirring in DMF (2 mL) was added HBTU (93 mg, 0.25 mmol). The resulting mixture was stirred under argon at room temperature for 80 minutes. The reaction was concentrated *in vacuo*, and the residue was partitioned between ethyl acetate and water. The organic phase was washed with water (4X), brine (1X), dried over anhydrous sodium sulfate, filtered and evaporated to give the crude product which was flash chromatographed on silica gel (10 g) eluted with 0-5% methanol in methylene chloride to give the title compound as a mixture of diastereomers. LC-MS M+H$^+$ = 458.

69b.) Furan-2-carboxylic acid {(S)2-cyclopentyl-1-[1-(1-furan-2-yl-methanoyl)-3-oxo-azepan-4-ylcarbamoyl]-ethyl}-amide

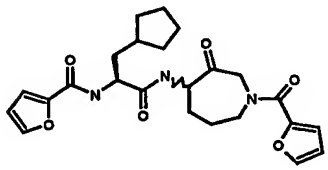
Following the procedure of Example 61i, except substituting furan-2-carboxylic acid {(S)-2-cyclopentyl-1-[1-(1-furan-2-yl-methanoyl)-3-hydroxy-azepan-4-ylcarbamoyl]-ethyl}-amide (the product of Example 69a) for 4-{(S)-3-cyclopentyl-2-[(1-furan-2-yl-methanoyl)-amino-propanoylamino}-3-hydroxy-azepane-1-carboxylic acid benzyl ester. gave the title compound as a mixture of diastereomers. LC-MS M+H$^+$ = 456.

69c.) Furan-2-carboxylic acid {(S)2-cyclopentyl-1-[1-(1-furan-2-yl-methanoyl)-3-oxo-azepan-4-ylcarbamoyl]-ethyl}-amide (first diastereomer eluted)

The mixture of diastereomers from Example 69b was separated on a preparative R,R Whelk-O column. The first diastereomer eluted, an off-white amorphous solid, was the title compound. mp 88-89°C; LC-MS M+H$^+$ = 456; ^{1}H NMR (400Hz, $CDCl_3$): δ 7.48-7.55 (m, 2H), 7.14-7.24 (m, 2H), 6.98 (m, 1H), 6.80 (m, 1H), 6.52-6.55(m, 2H), 5.4 (m, 1H), 4.60-4.90 (m, 4H), 3.70 (m, 1H), 1.18-2.30 (m, 15H).

Example 70

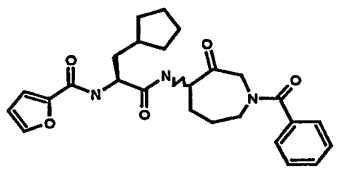
Preparation of 70: Furan-2-carboxylic acid {(S)-2-cyclopentyl-1-[1-(1-furan-2-yl-methanoyl)-3-oxo-azepan-4-ylcarbamoyl]-ethyl}-amide (second diastereomer eluted)



The mixture of diastereomers from Example 69b was separated on a preparative R,R Whelk-O column. The second diastereomer eluted, an off-white amorphous solid, was the title compound. mp 85-88°C; LC-MS M+H$^+$ = 456; ^{1}H NMR (400Hz, $CDCl_3$): δ 7.47-7.52 (m, 2H), 7.14-7.19 (m, 3H), 6.75-6.76 (m, 1H), 6.51-6.53 (m, 2H), 5.20-5.30 (m, 1H), 4.61-4.67 (m, 4H), 3.65-3.95 (m, 1H), 1.18-3.05 (m, 15H).

Example 71

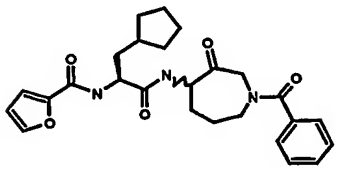
Preparation of 71: Furan-2-carboxylic acid {(S)-2-cyclopentyl-1-[3-oxo-1-(1-phenyl-methanoyl)-azepan-4-ylcarbamoyl]-ethyl}-amide (first diastereomer eluted)



Following the procedure of Example 69 (a-c) except substituting benzoic acid for furan-2-carboxylic acid in step 69a gave the title compound, as the first diastereomer eluted. mp 101-103°C; LC-MS M+H$^+$ = 466; ^{1}H NMR (400Hz, $CDCl_3$): δ 7.48 (m, 5H), 7.14-7.15 (m, 1H), 6.75-6.76 (m, 1H), 7.03 (m, 1H), 6.83 (m, 1H) 6.52-6.53 (m, 1H) 5.30-5.40 (m, 1H), 3.64-4.79 (m, 5H), 1.18-3.05 (m, 15H).

Example 72

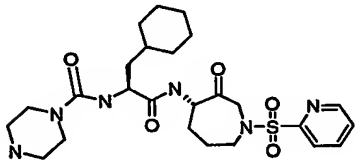
Preparation of 72: Furan-2-carboxylic acid {(S)-2-cyclopentyl-1-[3-oxo-1-(1-phenyl-methanoyl)-azepan-4-ylcarbamoyl]-ethyl}-amide (second diastereomer eluted)



Following the procedure of Example 69 (a-c) except substituting benzoic acid for furan-2-carboxylic acid in step 69a gave the title compound, as the second diastereomer eluted. mp 97-100°C; LC-MS M+H$^+$ = 466; ^{1}H NMR (400Hz, $CDCl_3$): δ 7.20-7.45 (m, 6H), 7.14-7.15 (m, 1H), 7.03 (m, 1H), 6.82-6.84 (m, 1H) 6.51-6.52 (m, 1H) 5.20-5.40 (m, 1H), 3.64-4.90 (m, 5H), 1.18-3.05 (m, 15H).

Example 73

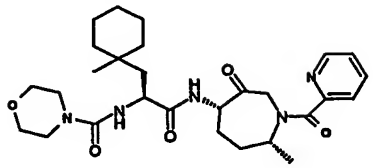
Preparation of 73: Piperazine-1-carboxylic acid {(S)-2-cyclopentyl-1-[(4S, 7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide



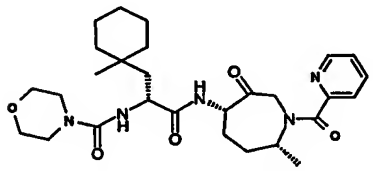
Following the general procedure described in Example 37c, (S)-2-amino-3-cyclohexyl-N-[(3S, 4S)-3-hydroxy-1-(pyridine-2-sulfonyl)-azepan-4-yl]-propionamide HCl salt (Example 38g, 150 mg, 0.33 mmol) was coupled with 4-(1-imidazol-1-yl-methanoyl)-piperazine-1-carboxylic acid tert-butyl ester methyl iodide salt (Example 37b, 139mg, 0.33mmol) to give the 3-hydroxy intermediate. Upon oxidation with Dess-Martin periodinane (182mg, 0.43mmol) followed by removal of the tert-butoxycarbonyl protecting group with 4N HCl the title compound was obtained (8mg, 4%). LC-MS m/z 535.2 (M$^+$), 1.45 min.

Example 74

Preparation of 74A: morpholine 4-carboxylic acid {(S)-2-[1-methylcyclohexyl-1-(4S,7R)-7-methyl-3-oxo-1-(1-pyridin-2-yl-meyhanoyl)-azepan-4-ylcarbamoyl]-ethyl}-amide



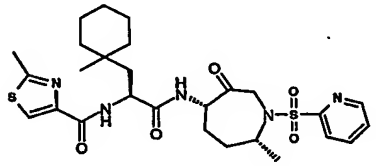
Preparation of 74B: morpholine 4-carboxylic acid {(L)-2-[1-methylcyclohexyl-1-(4S,7R)-7-methyl-3-oxo-1-(1-pyridin-2-yl-methanoyl)-azepan-4-ylcarbamoyl]-ethyl}-amide



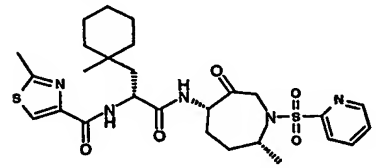
Following the procedure of Example 1 (b-r), except substituting "1-pyridin-2-yl-methanoyl " for "1-oxy-pyridine-2-sulfonyl" gave the title compound: ^{1}HNMR data of 74A: ^{1}H NMR (400Hz, $CDCl_3$): δ 8.4 (d, 1H), 7.65 (m, 2H), 7.35 (m, 1H), 6.95 (d, 1H), 5.35 (m, 1H), 4.97 (m, 2H), 4.55 (d, 1H), 4.45 (m, 1H), 3.80 (d, 1H), 3.70 (t, 4H), 3.35 (t, 4H), 2.4 (m, 1H), 2.15 (m, 1H), 0.95-1.9 (m, 18H). The ^{1}H NMR data of 75B:^{1}H NMR (400Hz, $CDCl_3$): δ 8.5 (d, 1H), 7.82 (m, 2H), 7.35 (m, 1H), 7.1 (d, 1H), 5.25 (m, 1H), 4.97 (m, 2H), 4.6 (d, 1H), 4.45 (m, 1H), 3.80 (d, 1H), 3.70 (t, 4H), 3.35 (t, 4H), 2.4 (m, 1H), 2.15 (m, 1H), 0.95-1.9 (m, 18H).

Example 75

Preparation of 75A: 2-Methyl-thiazole-4-carboxylic acid {(S)-2-[1-methylcyclohexyl-1-(4S,7R)-7-methyl-3-oxo-1-(1-pyridin-2-yl-meyhanoyl)-azepan-4-ylcarbamoyl]-ethyl}-amide



Preparation of 74B: 2-Methyl-thiazole-4-carboxylic acid {(L)-2-[1-methylcyclohexyl-1-(4S,7R)-7-methyl-3-oxo-1-(1-pyridin-2-yl-methanoyl)-azepan-4-ylcarbamoyl]-ethyl}-amide



Following the procedure of Example 3 (f-r), except substituting "2-Methyl-thiazole-4-carboxylic acid " for "morpholine-4-carboxylic acid " gave the title compound: ^{1}HNMR data of

74A: ^{1}H NMR (400Hz, $CDCl_3$): δ 8.7 (d, 1H), 8.08 (d, 1H), 7.92 (s, 1H), 7.6 (d, 1H), 7.54 (d, 1H), 6.88 (d, 1H), 5.1 (m, 1H), 4.6 (m, 1H), 4.2 (d, 1H), 4.0 (m, 2H), 3.8 (m, 1H), 3.4 (d, 1H), 2.7 (s, 3H), 2.2 (m, 2H), 0.9-1.7 (m, 19H). The ^{1}H NMR data of 75B: ^{1}H NMR (400Hz, $CDCl_3$): δ 8.7 (d, 1H), 8.1 (d, 1H), 7.92 (s, 1H), 7.65 (d, 1H), 7.52 (d, 1H), 6.9 (d, 1H), 5.10 (m, 1H), 4.6 (m, 1H), 4.1 (d, 1H), 4.0 (m, 2H), 3.8 (m, 1H), 3.4 (d, 1H), 2.7 (s, 3H), 2.2 (m, 2H), 0.9-1.7 (m, 19H).